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Your reference	ITT0055PV	
Patent application number 04 APR 2003 (The Patent Office will fill in this part)	0307891.2	07APR03 E798047-1 D02639 P01/7700 0.00-0307891.2
Full name, address and postcode of the or of each applicant (underline all surnames)	Istituto Di Ricerche Di Biologia Molecolare P Angeletti SpA Via Pontina KM 30.600 I-00040 Pomezia (Rome) Italy	
07557036002 Patents ADP number (if you know it)		
If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom	
Title of the invention	Chemical compounds, compositions and uses	
Name of your agent (if you have one)	Dr. W. G. Cole	
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	Merck & Co., Inc. European Patent Department Terlings Park Eastwick Road Harlow Essex CM20 2QR	
Patents ADP number (if you know it)	01010289001 01010529002	

If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority Application number (if you know it)	Date of filing (day/month/year)

If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if: any applicant named in part 3 is not an inventor, or there is an inventor who is not named as an applicant, or any named applicant is a corporate body. See note (d))	Yes

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Request for preliminary examination and search (Patents Form 9/77)	-
Request for substantive examination (Patents Form 10/77)	-
Any other documents (please specify)	-

I/We request the grant of a patent on the basis of this application.

Signature Dr. W. G. Cole Date 04 April 2003

. Name and daytime telephone number of person to contact in the United Kingdom Dr. W. G. Cole 01279 440163

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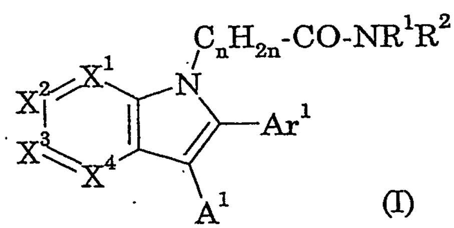
CHEMICAL COMPOUNDS, COMPOSITIONS AND USES

The present invention relates to indole and azaindole compounds, to pharmaceutical compositions containing them, to their use in the prevention and treatment of hepatitis C infections and to methods of preparation of such compounds and compositions.

Hepatitis C (HCV) is a cause of viral infections. There is as yet no adequate treatment for HCV infection but it is believed that inhibition of its RNA polymerase in mammals, particularly humans, would be of benefit. International patent applications WO 01/47883, WO 02/04425 and WO 03/000254 suggest fused ring compounds as possible inhibitors of HCV polymerase and illustrate thousands of possible benzimidazole derivatives that possess HCV polymerase inhibitory properties. However, these patent applications do not describe or reasonably suggest the preparation of any benzimidazole or azabenzimidazole substituted on all three available sites on the fused imidazole ring. WO 03/010140 and WO 03/010141 suggest further fused ring compounds as possible inhibitors of HCV polymerase and illustrate thousands of possible compounds all of which possess complex esterified side chains. The corresponding acids are suggested as intermediates only and not as HCV polymerase inhibitors. In particular none of these patent applications describe an indole or azaindole in which the indole nitrogen is substituted by an alkylamide residue.

The present invention provides compounds of the formula (I):



(I)

wherein:

Ar^1 is a moiety containing at least one aromatic ring and possesses 5-, 6-, 9- or 10-ring atoms 0 to 3 of which may be N, O or S heteroatoms of which at most 1 will be O or S; which moiety may be optionally substituted by groups Q_1, Q_2 or Q_3 wherein Q_1 is a hydroxy group, or a hydrogen, fluorine, chlorine, bromine or iodine atom or a C_{1-6} alkyl, C_{1-6} alkyl substituted by not more than 5 fluorine atoms, C_{1-6} alkoxyl, C_{1-6} alkoxyl substituted by not more than 5 fluorine atoms, C_{2-6} alkenyl or alkynyl, nitro, nitrile, carboxyl, esterified carboxy wherein the esterifying moiety has up to 4 carbon atoms optionally substituted by not more than 5 fluorine atoms,

Q_2 is a fluorine or chlorine atom or a methyl, trifluoromethyl, methoxy, trifluoromethoxyl or difluoromethoxy group.

Q_3 is a fluorine or chlorine atom or a methyl, methoxyl, trifluoromethoxy or difluoromethoxy group;

or Ar^1 is a group disclosed as a substituent on the G^6 moiety of the compound of formula (I) of WO 01/47883 which is incorporated herein by cross reference;

X^1 is N or CR^a; X^2 is N or CR^3; X^3 is N or CR^4; X^4 is N or CR^b; with the proviso that at least one of X^2 and X^3 is not N; wherein R^a and R^b are independently selected from hydrogen, fluorine or chlorine or C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkyl or alkoxy optionally substituted by up to 6 fluorine atoms and/or a hydroxyl group;

n is 1, 2, 3, 4, 5 or 6;

R^1 and R^2 are independently hydrogen, a group Ar^2, C_{1-6} alkyl, C_{2-6} alkenyl or a C_{1-6} alkyl or C_{2-6} alkenyl group substituted by 1-3 fluorine atoms or a OR^7, NR^7R^8, CO_2H, Ar^2 or A^2 group or R^1 and R^2 are joined to form a ring of 3 to 8 ring atoms, 1 or 2 of which ring atoms may be selected from N, O, S, SO, or SO_2 moieties, which ring may be substituted by a group Ar^2, A^2, C_{1-6} alkyl, C_{1-6} alkyl Ar^2, C_{1-6} alkyl

A^2, or a further ring of 5-6 ring atoms 1 or 2 of which may be selected from N, O, S which further ring may be substituted by C_{1-6} alkyl substituted by 1-3 fluorine atoms, OR^7, NR^7R^8 or CO_2H group; R^7 is hydrogen or C_{1-6} alkyl, R^8 is hydrogen, C_{1-4} alkyl optionally substituted by hydroxy, carboxy, amino, monoC_{1-6} alkyl or diC_{1-6} alkyl wherein the alkyl groups may be joined to form a 5- or 6-membered unsaturated ring which may contain a O, S, NH or NCH_3 group;

Ar^2 is a moiety containing at least one aromatic ring and possesses 5-, 6-, 9- or 10-ring atoms 0 to 3 of which atoms may be N, O or S heteroatoms of which at most 1 will be O or S; which aromatic ring may be optionally substituted by groups Q_1', Q_2' or Q_3' wherein Q_1' is a hydroxy group, or a hydrogen, fluorine, chlorine, bromine or iodine atom or a C_{1-6} alkyl, C_{1-4} alkyl substituted by not more than 5 fluorine atoms, C_{1-6} alkoxyl, C_{1-4} alkoxyl substituted by not more than 5 fluorine atoms, C_{2-6} alkenyl or alkynyl, nitro, nitrile, carboxyl, esterified carboxy wherein the esterifying moiety has up to 4 carbon atoms optionally substituted by not more than 5 fluorine atoms,

Q_2' is a fluorine or chlorine atom or a methyl, trifluoromethyl, methoxy, trifluoromethoxyl or difluoromethoxy group.

Q_3' is a fluorine or chlorine atom or a methyl, methoxyl, trifluoromethoxy or difluoromethoxy group;

A^1 is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkyl or C_{2-6} alkenyl substituted by C_{1-4} alkoxy or up to 5 fluorine atoms or a non-aromatic ring of 3 to 8 ring atoms which may contain a double bond and which may contain a O, S, SO, SO_2 or NH moiety and which may be optionally substituted by one or two alkyl groups of up to 2 carbon atoms or by 1 to 8 fluorine atoms;

A^2 is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkyl or C_{2-6} alkenyl substituted by C_{1-4} alkoxy or up to 5 fluorine atoms or a non-aromatic ring of up to

8 ring atoms which may contain a double bond and which may contain a O, S, SO, SO_2 or NH moiety and which may be optionally substituted by one or two alkyl groups of up to 2 carbon atoms or by 1 to three fluorine atoms;

one of R^3 and R^4 is a Het or is hydrogen, fluorine, chlorine or bromine atom or a C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} alkyl or alkoxy substituted by up to 5 fluorine atoms, nitrile, carboxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkyl or C_{2-4} alkenyl substituted by a carboxy or C_{1-4} alkoxycarbonyl group, or a $SO_2NR^9R^{10}$ or $CONR^9R^{10}$ group where R^9 is hydrogen, C_{1-4} alkyl, SO_2R^{11} or COR^{11} and R^{10} is hydrogen, hydroxyl or C_{1-4} alkyl or R^9 and R^{10} are alkylene linked to form a 5- or 6-membered ring, and R^{11} is C_{1-4} alkyl optionally substituted by up to 5 fluorine atoms or a group independently chosen from within the definitions of the Ar^2 group;

Het is a 5 or 6-membered aromatic ring 1, 2 or 3 of which may be selected from N, O, S which ring may be substituted by 1 or 2 groups selected C_{1-4} alkyl or hydroxy or tautomers thereof, or is 2-hydroxy-cyclobutene-3,4-dione;

the other of R^3 and R^4 is a hydrogen, fluorine or chlorine atom or C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} alkyl or alkoxy substituted by up to 6 fluorine atoms and optionally a hydroxyl; and

or a pharmaceutically acceptable salt thereof.

The group C_nH_{2n} may be straight or branched such as a $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)-$, $-CH_2-CH(CH_3)-$, $-CH(CH_3)-CH_2-$ or the like straight or branched butyl, pentyl or hexyl group. Most suitably the C_nH_{2n} group is a $-CH_2-$ group.

When used herein C_{1-6} alkyl means methyl, ethyl, 1-propyl, 2-propyl or a straight or branched butyl, pentyl or hexyl group. Particularly apt C_{1-6} alkyl groups are methyl, ethyl, propyl and butyl groups. Favoured

alkyl groups are ethyl and methyl groups. The methyl group is the preferred alkyl group.

Most suitably a C_{1-6} alkyl group substituted by up to 5 fluorine atoms will include a CF_3, CHF_2 and/or CF_2 moiety. Favoured fluoroalkyl groups are the CF_3, CH_2F and CF_2CF_3 groups. The CF_3 group is the preferred fluoroalkyl group.

When used herein C_{2-6} alkenyl means a $-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=C(CH_3)$, $-C(CH_3)=C(CH_3)$ or straight or branched pentylene or hexylene groups.

When used herein C_{1-6} alkoxy and fluorinated C_{1-6} alkoxy are analogous to the alkyl and fluoroalkyl groups described above so that, for example, preferred groups include OCH_3, OCF_3 and $OCHF_2$ groups.

Favoured values for R^a and R^b independently include hydrogen, fluorine, methyl, methoxy and trifluoromethyl. Particularly apt values for R^a and R^b include hydrogen or fluorine. A preferred value for R^a is hydrogen. A preferred value for R^b is hydrogen.

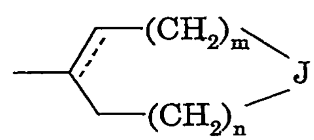
The Ar^1 moiety may contain a single aromatic ring or one aromatic ring to which a further aromatic or non-aromatic ring is fused.

Ar^1 is aptly phenyl, naphthyl, indinyl, tetrahydronaphthyl, pyridyl, furyl, thienyl, pyrolidyl, oxazolyl, thiazolyl, pyrazolyl, pyridazolyl, triazolyl, oxadiazolyl, thiodiazolyl or quinonyl, any of which may be optionally substituted by group Q^1, Q^2 or Q^3 as hereinbefore defined.

Favourably, Ar^1 is a furyl or thienyl group or a group of the formula $C_6H_2Q^1Q^2Q^3$. One particularly favoured group Ar^1 is the furyl group,

Other particularly favoured Ar^1 groups are optionally substituted phenyl groups of the formula $C_6H_3Q^1Q^2$ of which phenyl, fluorophenyl, chlorophenyl, hydroxyphenyl, trifluoromethylphenyl, methoxyphenyl, difluorophenyl and the like are preferred.

Particularly suitable groups A^1 include those groups of the formula



wherein m + n is 0, 1, 2, 3 or 4, preferably 1 or 2, the dotted line represents an optional double bond and J is CH_2, O, S, SO, SO_2 or NH which group of the above formula may optionally be substituted by one or two methyl groups.

Favoured groups A^1 include cycloalkyl and cycloalkenyl groups of 5 or 6 ring members.

A preferred group A^1 is the cyclohexyl group.

Particularly apt compounds of this invention include those wherein one of R^3 and R^4 is a carboxy or $-Y-CO_2H$ group wherein Y is CH_2, CH_2CH_2 or CH:CH group, or a pharmaceutically acceptable salt thereof.

A preferred group R^3 is the CO_2H group or a pharmaceutically acceptable salt thereof.

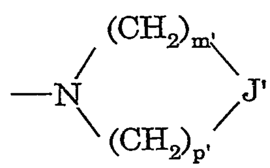
Favourably one of R^3 and R^4 is a hydrogen atom.

Certain favoured compounds of the invention include those wherein R^4 is hydrogen, fluorine or chlorine of which hydrogen is preferred.

A favoured value for X_4 is CH.

In those compounds of formula (I) wherein R^1 is a hydrogen atom or C_{1-4}alkyl group R^2 may aptly be a hydrogen atom or a C_{1-4} alkyl or a group C_{1-4} alkyl Ar^2 group wherein the Ar^2 group is as hereinbefore defined wherein Q^2 and Q^3 are hydrogen atoms.

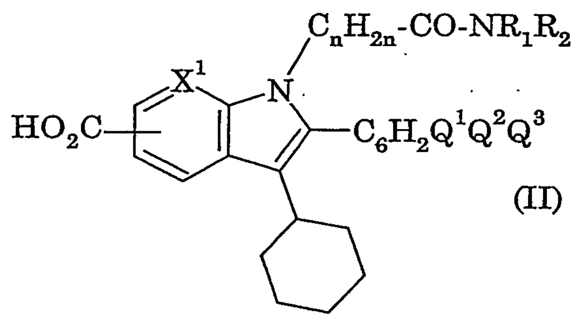
In those compounds of formula (I) wherein R^1 and R^2 are linked they aptly form an optionally substituted ring of the formula:



wherein J' is CH_2, NH, O, S, SO, or SO_2 and m' + p' is 1 to 6, more aptly 2 to 5 and preferably 3 or 4 and where the one or two optional substituents are selected from C_{1-4} alkyl and hydroxy and Ar^2 where the Ar^2 group is as hereinbefore defined or a fused pendent or spiro 5 or 6 membered ring in which one of the ring moieties may be a O, NH or NCH_3 group.

Favoured values for A^1 include non-aromatic rings. Such rings are aptly of 5 or 6 carbon atoms and which are saturated or monounsaturated. Preferred groups A^1 include cyclopentyl, cyclohexyl and cyclohexenyl groups.

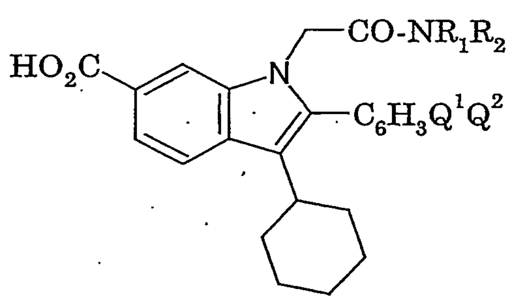
Certain particularly suitable compounds of the invention are represented by the formula (II):



(II)

wherein n, X^1, Q^1, Q^2, Q^3, R^1 and R^2 are as defined in relation to formula (I) or a pharmaceutically acceptable salt thereof.

In compounds of formula (I) and (II) a favoured value for Q^3 is H, a favoured value for n is 1 and a favoured value for X^1 is CH so that particularly apt compounds of the invention include those of formula (III):



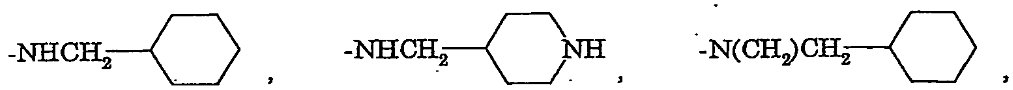
(III)

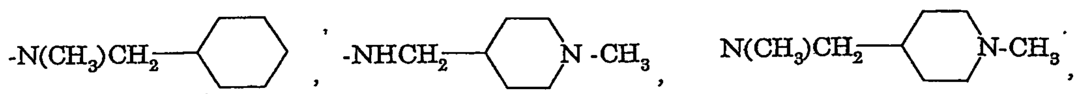
wherein Q^1, Q^2, R^1 and R^2 are defined in relation to formula (I) or a pharmaceutically acceptable salt thereof.

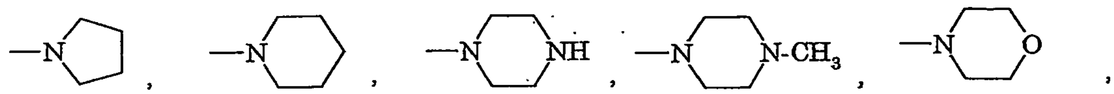
In certain apt compounds of formulas (II) and (III) Q^2 is hydrogen fluorine chlorine, methyl, methoxyl or trifluoromethyl. In certain apt compounds of formulas (II) and (III) Q^1 is hydrogen or fluorine. In certain preferred compounds of formulas (II) and (III) Q^1 is hydrogen and Q^2 is hydrogen or fluorine.

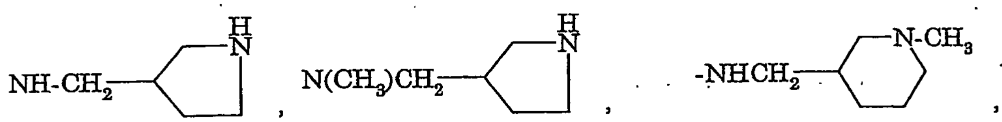
In compounds of formulae (I), (II) and (III) particularly apt values for NR^1R^2 are those wherein R^1 is hydrogen or methyl, R^2 is hydrogen, methyl or ethyl optionally substituted by (i) an aryl group of 5 or 6 ring atoms up to 3 of which may be selected from O, N or S of which not more than one may be O or S which aryl group may be substituted by a methyl or methoxy group; (ii) a 5 or 6 membered saturated ring which one ring atom may be a O, S or N atom and which ring may be substituted by a methyl group; or (iii) 2-substituted by a hydroxy, amino, methylamino or dimethylamino group; or R^1 and R^2 may be joined so that NR^1R^2 forms a 4 or 6 membered saturated ring of which one additional ring atom may be a O, S or N atom and which ring may be substituted by a methyl group.

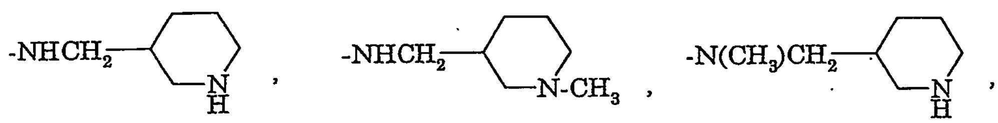
In compounds of formulae (I), (II) and (III) particularly suitable $-NR^1R^3$ groups include (wherein Py is pyridyl):
$-NH_2$, $-NH-CH_3$, $-NH-C_2H_5$, $-N(CH_3)_2$, $-N(CH_3)C_2H_5$, $-NHCH_2C_6H_5$, $-NH-CH_2C_6H_4F$, $-NH-CH_2C_6H_4OCH_3$, $-N(1CH_3)CH_2C_6H_5$, $-N(CH_3)CH_2C_6H_4F$, $-N(CH_3)CH_2C_6H_4OCH_3$,

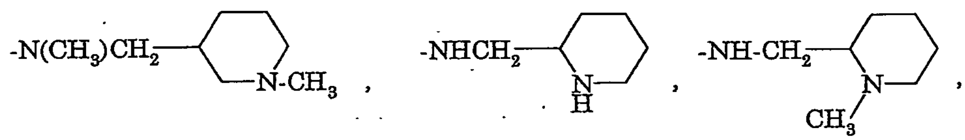


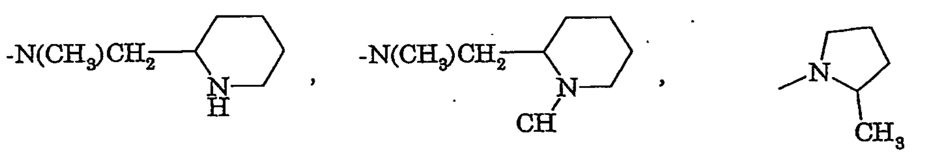


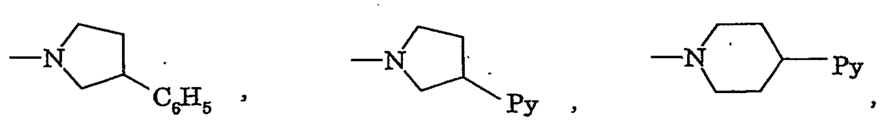


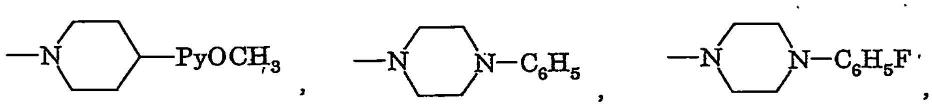




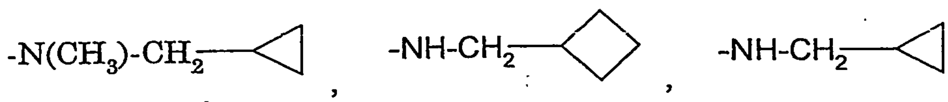








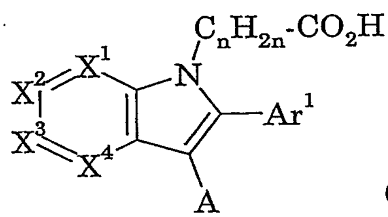
$-NH-C(CH_5)C_6H_5$, $-NH-C(CH_3)Py$, $-N(CH_3)C(CH_3)C_6H_5$, $-NH-CH_2CH{:}CH_2$, $-NH-CH_2C\equiv CH$, $N(CH_3)CH_2CH{:}CH_2$, $-N(CH_3)CH_2C\equiv CH$,



$-NH-CH_2CH_2NH_2$, $-NH-CH_2CH_2-N(CH_3)_2$, $-NH-CH_2CH_2-NHCH_3$, $N(CH_3)-CH_2CH_2NH_2$, $-N(CH_3)CH_2CH_2N(CH_3)_2$, $-NH-CH_2CH_2OH$.

The compounds of the formula (I) may be in the form of a pharmaceutically acceptable salt such as a sodium, potassium, calcium, magnesium or ammonium salt or a salt with a pharmaceutically acceptable organic base. If the compounds of the formula (I) also contain a group, the compound may be zwitterionic or in the form of a salt with a pharmaceutically acceptable acid such as hydrochloric, sulphuric, phosphoric, methane sulfonic and the like acid.

The present invention provides a process for the preparation of compounds of formula (I) and their salts which comprises the reaction of compounds of the formulas (IV) and (V):



(IV)

HNR^1R^2

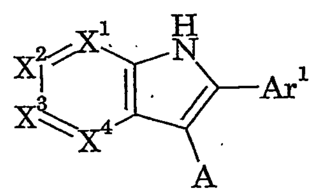
(V)

In the compounds of formulae (IV) and (V) any reactions group that requires masking during the amidation reaction may be protected in conventional manner and the protecting group removed thereafter.

This principle of utilising protecting groups also applies to all other reactions described hereinafter. For example, if the desired compound of the formula I contains a CO_2H group, then the compound of the formula (IV) may contain a CO_2CH_3 group and the resulting compound of the formula (I) may be hydrolysed in conventional manner, for example with sodium hydroxide in aqueous methanol or BBr_3 in DCM to yield the compound containing the carboxylate or its sodium salt. Similarly the substituents on the core bicycle may be elaborated after the amidation reaction, for example if the desired compound of formula (I) contains a

tetrazole group then the compound of formula (IV) may contain CN group and the resulting compound of formula (I) may be reacted with an azide.

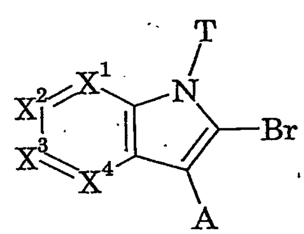
The compound of the formula (IV) may be prepared from the corresponding compound of the formula (VI):



(VI)

by reaction with 1-bromo ethanoic acid t-butyl ester under conventional conditions for forming an amide followed by de-esterification with trifluoroethanoic acid in DCM.

In an alternative process the compounds of formula (I) may be prepared from the corresponding compound of the formula (VII):

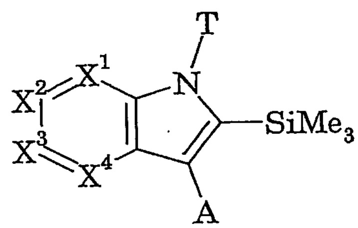


(VII)

wherein T is a $C_nH_{2n}CONR^1R^2$ group by reaction with $Ar^1B(OH)_2$ in the presence of a Pd[O] catalyst under conditions conventional for the Susuki reaction.

The compound of formula (VII) wherein T is a $C_nH_{2n}CONR^1R^2$ group can be prepared from the compound of formula (VII) wherein T is a hydrogen atom by reaction with 1-bromoethanoic acid t-butyl ester.

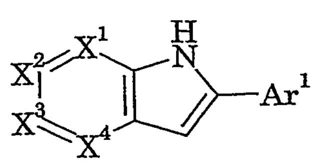
Alternatively the compound of formula (VII) may be prepared by the reaction of NBS and the compound of the formula (VIII):



(VIII)

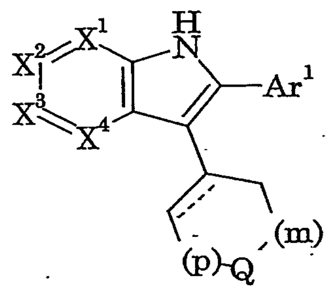
wherein T is $C_nH_{2n}CONR^1R^2$ which may itself be prepared from the corresponding compound of formula (VIII) wherein T is H by reaction with $BrC_nH_{2n}CONR^1R^2$ under conventional alkylation conditions.

In an alternative synthesis the compounds of the formula (VI) may be prepared from the reaction of corresponding compounds of the formulae (IX) and (X):

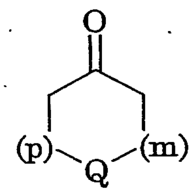


(IX) (X)

Similarly certain compounds of the formula (XI) may be prepared by the reaction of a compound of the formula (IX) with compounds of the formula (XII):



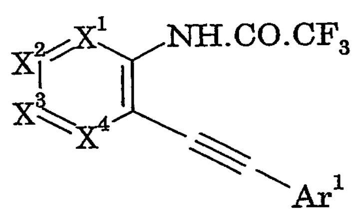
(XI)



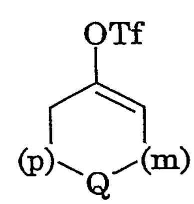
(XII)

wherein Q is CH_2, NH, O, S, SO or SO_2 and m + p is 1 or 2 and where one or two optional substituents are selected from C_{1-6} alkyl and hydroxyl and the dotted line is an optional double bond; optionally followed by reduction of said optional double bond.

The compounds of formula (XI) may also be prepared by the reaction of the compounds of the formulae (XIII) and (XIV):



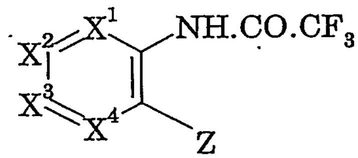
(XIII)



(XIV)

wherein Q, m and p are as defined in relation to formula (XII) in the presence of a Pd[O] catalyst optionally followed by reduction of the optional double bond.

The compound of the formula (XIII) may be prepared from the compounds of the formulae (XV) and (XVI):



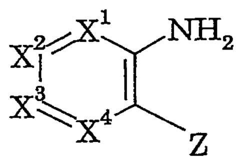
(XV)

$Ar^1 - C \equiv CH$

(XVI)

wherein Z is I, Br or OTf in the presence of a Pd[O] catalyst.

A further process for the preparation of the compounds of formula (VIII) wherein T is hydrogen comprises the reaction of the compounds of the formulae:



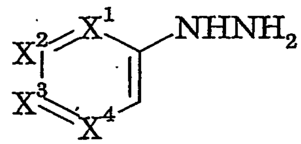
(XVII)

$Ar^1 - C \equiv C\text{-}SiMe_3$

(XVIII)

wherein Z is I, Br or OTf.

In addition, compounds of the formula (VI) may be prepared by the reaction of a hydrazine of the formula (XIX):



(XIX)

$Ar^1\text{-CO-}CH_2\text{-}A^1$

(XX)

and a ketone of the formula (XX).

The compounds of formulas (I)-(III) may be used for the inhibition of HCV polymerase and so may be used for the manufacture of medicaments which may be used to treat HCV infection.

Accordingly this invention provides a pharmaceutical composition comprising a compound of the formula (I) as hereinbefore described as a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a

pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of infection due to hepatitis C, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day. Most suitably the administration is orally using a unit done as previously indicated.

In a further aspect this invention provides the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of infection by hepatitis C

virus. Most suitably the medicament is in unit dose form adapted for oral administration as indicated hereinbefore..

In another aspect this invention provides the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of infection by hepatitis C virus in a mammal and preferably in a human. Most suitably the treatment is effected by oral administration of a unit dose form as indicated hereinbefore.

Useful references in the literature for synthetic preparations include: Nanomoto et al, J. Chem. Soc. Perkin I, 1990, III; Freter, J. Org. Chem., 1975, 40, 2525; Cacchi et al, Eur. J. Org. Chem., 2002, 2671; Ujjainwalla, Tetrahedron Lett., 1998, 39, 5355; Wang et al, J. Org. Chem., 2000, 65, 1889; Larock, J. Org. Chem., 1998, 63, 7652; Kelly et al, J. Org. Chem., 1996, 61, 4623; and Cacchi, Tetrahedron Lett., 1992, 33, 3915.

The following Examples are illustrative of this invention.

The compounds of the invention were tested for inhibitory activity against the HCV RNA dependent RNA polymerase (NS5B) in an enzyme inhibition assay (example i)) and an cell based sub-genomic replication assay (describe in example ii)). The compounds generally have IC50's below 5 μM in the enzyme assay and EC50's below 20 μM in the cell based assay. For example -(2-{methyl[(1-methylpiperidin-2-yl)methyl]amino}-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid trifluoroacetate had an IC_{50} of 14 nM in the enzyme assay and an EC50 of 270 nM in the cell based assay.

<u>i) In-vitro HCV NS5B Enzyme Inhibition Assay</u>

WO 96/37619 describes the production of recombinant HCV RdRp from insect cells infected with recombinant baculovirus encoding the enzyme. The purified enzyme was shown to possess *in vitro* RNA polymerase

activity using RNA as template. The reference describes a polymerisation assay using poly(A) and oligo(U) as a primer or an heteropolymeric template. Incorporation of tritiated UTP or NTPs is quantified by measuring acid-insoluble radioactivity. The present inventors have employed this assay to screen the various compounds described above as inhibitors of HCV RdRp.

Incorporation of radioactive UMP was measured as follows. The standard reaction (50 µl) was carried out in a buffer containing 20 mM tris/HCl pH 7.5, 5 mM $MgCl_2$, 1 mM DTT, 50 mM NaCl, 0.03% N-octylglucoside, 1 µCi [^{3}H]-UTP (40 Ci/mmol, NEN), 10 µM UTP and 10 µg/ml poly(A) or 5µM NTPs and 5µg/ml heteropolymeric template. Oligo(U)$_{12}$ (1 µg/ml, Genset) was added as a primer in the assay working on Poly(A) template. The final NS5B enzyme concentration was 5 nM. The order of assembly was: 1) compound, 2) enzyme, 3) template/primer, 4) NTP. After 1 h incubation at 22 °C the reaction was stopped by adding 50 µl of 20% TCA and applying samples to DE81 filters. The filters were washed thoroughly with 5% TCA containing 1M Na_2HPO_4/NaH_2PO_4, pH 7.0, rinsed with water and then ethanol, air dried, and the filter-bound radioactivity was measured in the scintillation counter. Carrying out this reaction in the presence of various concentrations of each compound set out above allowed determination of IC_{50} values by utilising the formula:

$$\% \text{ Residual activity} = 100/(1+[I]/IC_{50})^S$$

where [I] is the inhibitor concentration and "s" is the slope of the inhibition curve.

ii) Cell based HCV Replication Assay

Cell clones that stably maintain subgenomic HCV replicon were obtained by transfecting Huh-7 cells with an RNA replicon identical to I_{377}neo/NS3-3'/wt described by Lohmann *et al.* (1999) (EMBL-genbank No. AJ242652),

followed by selection with neomycin sulfate (G418). Viral replication was monitored by measuring the expression of the NS3 protein by an ELISA assay performed directly on cells grown in 96 wells microtiter plates (Cell-ELISA) using the anti-NS3 monoclonal antibody 10E5/24 (as described by *De Francesco, Raffaele; Migliaccio, Giovanni; Paonessa, Giacomo. Hepatitis C virus replicons and replicon enhanced cells. PCT Int. Appl. WO 0259321 A2 20020801)*. Cells were seeded into 96 well plates at a density of 10^4 cells per well in a final volume of 0.1 ml of DMEM/10% FCS. Two hours after plating, 50 μl of DMEM/10% FCS containing a 3x concentration of inhibitor were added, cells were incubated for 96 hours and then fixed for 10' with ice-cold isopropanol. Each condition was tested in duplicate and average absorbance values were used for calculations. The cells were washed twice with PBS, blocked with 5% non-fat dry milk in PBS + 0.1% Triton X100 + 0.02% SDS (PBSTS) and then incubated o/n at 4^0 C with the 10E5/24 mab diluted in Milk/PBSTS. After washing 5 times with PBSTS, the cells were incubated for 3 hours at room temperature with Fc specific anti-mouse IgG conjugated to alkaline phosphatase (Sigma), diluted in Milk/PBSTS. After washing again as above, the reaction was developed with p-Nitrophenyl phosphate disodium substrate (Sigma) and the absorbance at 405/620 nm read at intervals. For calculations, we used data sets where samples incubated without inhibitors had absorbance values comprised between 1 and 1.5. The inhibitor concentration that reduced by 50% the expression of NS3 (IC_{50}) was calculated by fitting the data to the Hill equation,

$$\text{Fraction inhibition} = 1-(Ai-b)/(A_0-b) = [I]^n / ([I]^n + IC_{50})$$

where:

- Ai = absorbance value of HBI10 cells supplemented with the indicated inhibitor concentration.
- A_0 = absorbance value of HBI10 cells incubated without inhibitor.
- b = absorbance value of Huh-7 cells plated at the same density in the same microtiter plates and incubated without inhibitor.

- n = Hill coefficient.

iii) General Procedures

All solvents were obtained from commercial sources (Fluka, puriss.) and were used without further purification. With the exception of routine deprotection and coupling steps, reactions were carried out under an atmosphere of nitrogen in oven dried (110 °C) glassware. Organic extracts were dried over sodium sulfate, and were concentrated (after filtration of the drying agent) on rotary evaporatorators operating under reduced pressure. Flash chromatography was carried out on silica gel following published procedure (W.C. Still *et al.*, J. Org. Chem. **1978**, *43*, 2923) or on commercial flash chromatography systems (Biotage corporation and Jones Flashmaster) utilising pre-packed columns.

Reagents were usually obtained directly from commercial suppliers (and used as supplied) but a limited number of compounds from in-house corporate collections were utilised. In the latter case the reagents are readily accessible using routine synthetic steps that are either reported in the scientific literature or are known to those skilled in the art.

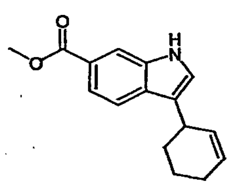
^1H nmr spectra were recorded on Bruker AM series spectrometers operating at (reported) frequencies between 300 and 600 MHz. Chemical shifts (δ) for signals corresponding to non-exchangeable protons (and exchangeable protons where visible) are recorded in parts per million (ppm) relative to tetramethylsilane and are measured using the residual solvent peak as reference. Signals are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad, and combinations thereof); coupling constant(s) in hertz; number of protons. Mass spectral (MS) data were obtained on a Perkin Elmer API 100 operating in negative (ES^-) or positive (ES^+) ionization mode and results are reported as the ratio of mass over charge (m/z) for the parent ion only. Preparative scale HPLC separations were carried out on a Waters Delta Prep 4000 separation module, equipped with a Waters 486 absorption

detector or on a Thermoquest P4000 equipped with a UV1000 absorption detector. In all cases compounds were eluted with linear gradients of water and acetonitrile both containing 0.1% TFA using flow rates between 15 and 25 mL/min.

The following abbreviations are used in the examples, the schemes and the tables:

DIEA: diisopropylethyl amine; DMF: dimethylformamide; DMSO: dimethylsulfoxide; eq.: equivalent(s); AcOEt: ethyl acetate; Et_2O: diethyl ether; MeCN: acetonitrile; h: hour(s); HATU: O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophophate; Me: methyl; EtOH: ethanol; min: minutes; NBS: *N*-bromo succinimide; Ph: phenyl; HPLC: reversed phase high-pressure liquid chromatography; TFA: trifluoroacetic acid; THF: tetrahydrofuran; MeOH: methanol; DME: Ethylene glycol dimethyl ether; TMS: trimethylsilyl.

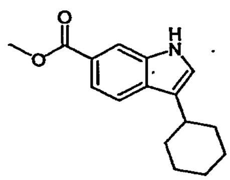
Example 1 : 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(4-methylphenyl)-1*H*-indole-6-carboxylic acid



<u>*Step 1*: methyl 3-cyclohex-2-en-1-yl-1*H*-indole-6-carboxylate</u>

A solution (0.2 M) of methyl 1*H*-indole-6-carboxylate in DMF was cooled to 0 °C then treated with LiH (1.3 eq.). The mixture was stirred for 0.5 h then warmed to 20 °C. A solution (1.0 M) of 3-bromocyclohex-1-ene (1.5 eq.) in DMF was added and the mixture was stirred for 16 h. AcOEt and H_2O were added and the organic layer was separated then washed with aqueous HCl (1 N) and dried. Removal of the solvent gave a residue that was purified by flash chromatography on silica gel (5:95 AcOEt/petroleum ether) to afford the title compound (52%) as an oil.

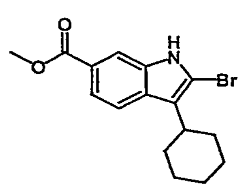
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ 1.61-1.85 (m, 4H), 2.05-1.18 (m, 2H), 3.71-3.75 (m, 1H), 3.94 (s, 3H), 5.80-5.95 (m, 2H), 7.14 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 8.12 (s, 1H), 8.20 (br s, 1H); MS (ES^+) m/z 256 $(M+H)^+$



Step 2: methyl 3-cyclohexyl-1*H*-indole-6-carboxylate

A solution (0.2 M) of methyl 3-cyclohex-2-en-1-yl-1*H*-indole-6-carboxylate in MeOH was treated with 10% Pd/C (10% wt.). The resulting suspension was stirred for 4 h under an atmosphere of hydrogen then purged with nitrogen and filtered. The filtrate was concentrated to afford the title compound (97%) as a solid.

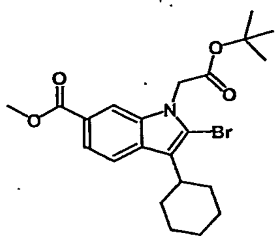
^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 1.22-1.24 (m, 2H), 1.39-1.51 (m, 3H), 1.69-1.81 (m, 3H), 1.95-2.00 (m, 2H), 2.75-2.81 (m, 1H), 3.83 (s, 3H), 7.33 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 8.00 (s, 1H), 11.16 (br s, 1H); MS (ES^+) m/z 258 $(M+H)^+$



Step 3: methyl 2-bromo-3-cyclohexyl-1*H*-indole-6-carboxylate

A solution (0.1 M) of methyl 3-cyclohexyl-1*H*-indole-6-carboxylate in CCl_4, was treated with NBS (1.1 eq.). The resulting mixture was stirred at 40 °C for 2 h, then the reaction was quenched by addition of 10% aqueous $Na_2S_2O_4$. The organic phase was separated and washed with brine, then dried. Removal of the solvent afforded a residue that was purified by flash chromatography on silica gel (5:95 AcOEt/petroleum ether) to afford the title compound (54%) as a solid.

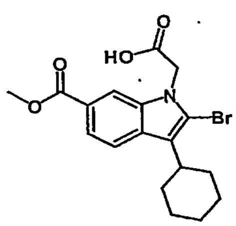
^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 1.32-1.49 (m, 3H), 1.64-2.00 (m, 7H), 2.73-2.88 (m, 1H), 3.84 (s, 3H), 7.61 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.90 (s, 1H), 12.02 (br s, 1H); MS (ES^+) m/z 336 $(M+H)^+$



Step 4: methyl 2-bromo-1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-1*H*-indole-6-carboxylate

A solution (0.1 M) of methyl 2-bromo-3-cyclohexyl-1*H*-indole-6-carboxylate in DMF was treated with NaH (1.3 eq.) and stirred for 0.5 h at 0 °C. The soluion was warmed to room temperature and treated with *tert*-butylbromoacetate (1.2 eq.) over 0.5 h. The mixture was stirred for 12 h then diluted with AcOEt and washed sequentially with aqueous HCl (1 N) and brine. The dried organic phase was concentrated and the residue purified by flash chromatography on silica gel (5:95 AcOEt/petroleum ether) to afford the title compound (83%) as a solid.

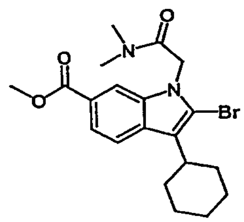
^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 1.31-1.50 (m, 3H), 1.40 (s, 9H), 1.64-1.80 (m, 3H), 1.81-2.04 (m, 4H), 2.80-2.92 (m, 1H), 3.86 (s, 3H), 5.09 (s, 2H), 7.66 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 8.13 (s, 1H); MS (ES$^+$) m/z 452 (M+H)$^+$



Step 5: [2-bromo-3-cyclohexyl-6-(methoxycarbonyl)-1*H*-indol-1-yl]acetic acid

A solution (0.05 M) of methyl 2-bromo-1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-1*H*-indole-6-carboxylate in a 1:1 mixture of CH_2Cl_2/TFA was stirred for 16 h. The mixture was concentrated and the residue triturated with Et_2O to afford the title compound (95%) as a solid.

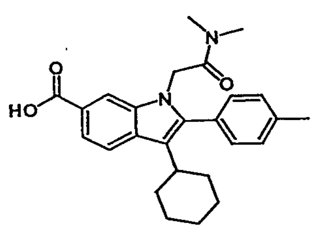
^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 1.30-1.50 (m, 3H), 1.64-1.78 (m, 3H), 1.79-2.02 (m, 4H), 2.79-2.90 (m, 1H), 3.86 (s, 3H), 5.10 (s, 2H,), 7.67 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 8.13 (s, 1H)



Step 6: methyl 2-bromo-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1*H*-indole-6-carboxylate

A solution (0.2 M) of [2-bromo-3-cyclohexyl-6-(methoxycarbonyl)-1*H*-indol-1-yl]acetic acid in DMF was treated with a dimethylamine hydrochloride (1.05 eq.) and HATU (1.05 eq.). The solution was cooled to 0 °C then treated with DIEA (4 eq.) then stirred for 12 h at 20 °C. The mixture was diluted with AcOEt then washed sequentially with aqueous HCl (1 N), saturated aqueous $NaHCO_3$ and brine. The dried organic layer was concentrated and the residue was purified by flash chromatography on silica gel (5:95 AcOEt/petroleum ether) to afford the title compound (90%) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 1.35-1.50 (m, 3H), 1.68-1.75 (m, 3H), 1.80-2.00 (m, 4H), 2.82-2.88 (m, 1H), 2.87 (s, 3H), 3.17 (s, 3H), 3.86 (s, 3H,), 5.26 (s, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 8.07 (s, 1H); MS (ES$^+$) m/z 421 $(M+H)^+$

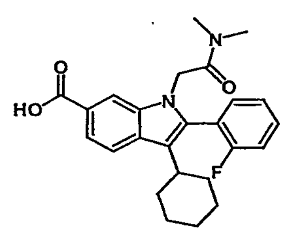


Step 7: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(4-methylphenyl)-1*H*-indole-6-carboxylic acid

A solution (0.1 M) of methyl 2-bromo-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1*H*-indole-6-carboxylate in DME and EtOH (5:2) was treated with 4-methylphenylboronic acid (1.2 eq.). Aqueous Na_2CO_3 (2 N, 8.5 eq.) was added and the solution was degassed, then treated with $Pd(PPh_3)_4$ (0.1 eq.). The mixture was heated at 80 °C for 4 h, then cooled and diluted with AcOEt and brine. The organic phase was separated and dried then

concentrated under reduced pressure. The residue was purified by filtration through silica gel (1:9 AcOEt/petroleum ether) to give a solid that was dissolved in CH_2Cl_2. The resulting solution (0.1 M) was treated dropwise with BBr_3 (3 eq.) then stirred at 20 °C for 2 h. The mixture was concentrated under reduced pressure and the residue was treated with aqueous HCl (1 N) then filtered. Purification by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 100 mm) gave the title compound (66%) as a solid.

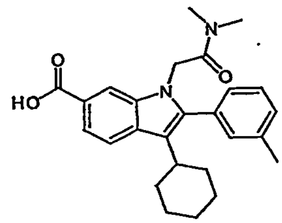
^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 1.09-1.42 (m, 3H), 1.59-1.99 (m, 7H), 2.41 (s, 3H), 2.48-2.65 (m, 1H), 2.83 (s, 3H), 2.93 (s, 3H), 4.86 (s, 2H), 7.21 (d, J = 7.3 Hz, 2H), 7.35 (d, J = 7.3 Hz, 2H), 7.66 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H), 12.60 (br s, 1H); MS (ES$^+$) m/z 419 (M+H)$^+$



Example 2: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(2-fluorophenyl)-1*H*-indole-6-carboxylic acid

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(4-methylphenyl)-1*H*-indole-6-carboxylic acid (step 7), treatment of methyl 2-bromo-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1*H*-indole-6-carboxylate with 2-fluorophenylboronic acid gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 100 mm) to afford the title compound (53%) as a solid.

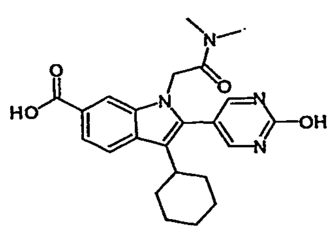
^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 1.10-1.40 (m, 3H), 1.60-1.90 (m, 7H), 2.39-2.62 (m, 1H), 2.77 (s, 3H), 2.91 (s, 3H), 4.62 (d, J = 17.5 Hz, 1H), 5.15 (d, J = 17.5 Hz, 1H), 7.26-7.48 (m, 3H), 7.54-7.64 (m, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 8.00 (s, 1H); MS (ES$^+$) m/z 423 (M+H)$^+$



Example 3: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(3-methylphenyl)-1*H*-indole-6-carboxylic acid

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(4-methylphenyl)-1*H*-indole-6-carboxylic acid (step 7), treatment of methyl 2-bromo-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1*H*-indole-6-carboxylate with 3-methylphenylboronic acid gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 100 mm) to afford the title compound (61%) as a solid.

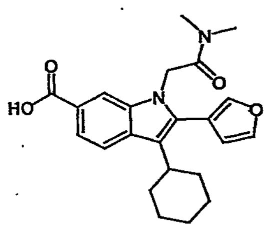
^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 1.11-1.41 (m, 3H), 1.60-2.00 (m, 7H), 2.39 (s, 3H), 2.48-2.66 (m, 1H), 2.83 (s, 3H), 2.91 (s, 3H), 4.86 (s, 2H), 7.07-7.20 (m, 2H), 7.32 (d, J = 7.3 Hz, 1H), 7.43 (t, J = 7.3 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.94 (s, 1H), 12.60 (s, 1H); MS (ES$^+$) m/z 419 (M+H)$^+$



Example 4: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(2-hydroxypyrimidin-5-yl)-1*H*-indole-6-carboxylic acid

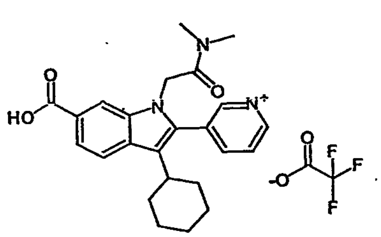
Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(4-methylphenyl)-1*H*-indole-6-carboxylic acid (step 7), treatment of methyl 2-bromo-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1*H*-indole-6-carboxylate with 2-methoxypyrimidin-5-ylboronic acid gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 100 mm; mobile phase:

linear gradient from 20% to 100% MeCN (containing 0.1% TFA) in H_2O (containing 0.1% TFA) over 10 min) to afford the title compound (21%) as a solid.
^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 1.22-1.40 (m, 3H), 1.62-1.90 (m, 7H), 2.45-2.62 (m, 1H), 2.83 (s, 3H), 3.06 (s, 3H), 5.05 (s, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 8.16 (s, 2H); MS (ES$^+$) m/z 423 (M+H)$^+$



Example 5: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(3-furyl)-1*H*-indole-6-carboxylic acid

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(4-methylphenyl)-1*H*-indole-6-carboxylic acid (step 7), treatment of methyl 2-bromo-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1*H*-indole-6-carboxylate with 3-furylboronic acid gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 100 mm; mobile phase: linear gradient from 20% to 100% MeCN (containing 0.1% TFA) in H_2O (containing 0.1% TFA) over 11 min) to afford the title compound (25%) as a solid.
^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 1.20-1.42 (m, 3H), 1.63-1.95 (m, 7H), 2.65-2.78 (m, 1H), 2.85 (s, 3H), 3.03 (s, 3H), 4.99 (s, 2H), 6.50 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H), 7.95 (s, 1H); MS (ES$^+$) m/z 395 (M+H)$^+$

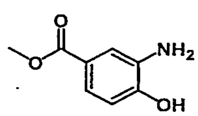


Example 6: 3-{6-carboxy-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1*H*-indol-2-yl}pyridinium trifluoroacetate

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(4-methylphenyl)-1*H*-indole-6-carboxylic acid (step 7), treatment of methyl 2-bromo-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1*H*-indole-6-carboxylate with 2-fluorophenyl boronic acid gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 100 mm; mobile phase: linear gradient from 20% to 100% MeCN (containing 0.1% TFA) in H_2O (containing 0.1% TFA) over 10 min) to afford the title compound (23%) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 1.15-1.40 (m, 3H), 1.62-1.92 (m, 7H), 2.45-2.58 (m, 1H), 2.79 (s, 3H), 2.95 (s, 3H), 4.96 (s, 2H), 7.68 (d, J = 8.4 Hz, 1H), 7.73 (dd, J = 7.6 and 4.8 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H) 8.01 (s, 1H), 8.62 (s, 1H), 8.78 (d, J = 4.8 Hz, 1H); MS (ES$^+$) m/z 406 (M+H)$^+$

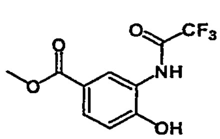
Example 7: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid



Step 1: methyl 3-amino-4-hydroxybenzoate

A solution (0.2 M) of acetyl chloride (3.0 eq.) in MeOH was prepared at 0 °C then allowed to warm to 20 °C. 3-amino-4-hydroxybenzoic acid (1.0 eq.) was added and the mixture was heated under reflux for 12 h then cooled and concentrated *in vacuo*. The residue was triturated with H_20 and dried to afford the title compound (99%) as a solid.

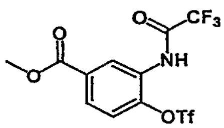
^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 3.83 (s, 3H), 7.15 (d, J = 8.5 Hz, 1H), 7.79 (dd, J = 2.1 Hz, J = 8.5 Hz, 1H), 7.93 (d, J = 2.1 Hz, 1H), 11.65 (br s, 1H)



Step 2: methyl 4-hydroxy-3-[(trifluoroacetyl)amino]benzoate

A solution (0.2 M) of methyl 3-amino-4-hydroxybenzoate in THF was cooled to 0 °C and treated dropwise with trifluoroacetic anhydride (2.0 eq.). The mixture was stirred at 0 °C for 2 h then at 20 °C for 1 h. The pH was adjusted to 7.5 by addition of saturated aqueous $NaHCO_3$ and the solution was extracted with AcOEt. The organic layer was washed with brine and dried, then concentrated to afford the title compound (87%) as a solid.

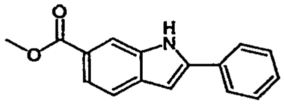
^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 3.82 (s, 3H), 7.02 (d, J = 8.5 Hz, 1H), 7.77 (dd, J = 2.1 Hz, J = 8.5 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 10.82 (br s, 1H)



Step 3: methyl 3-[(trifluoroacetyl)amino]-4-{[(trifluoromethyl)sulfonyl]oxy}benzoate

A solution (0.8 M) of methyl 4-hydroxy-3-[(trifluoroacetyl)amino]benzoate in dry pyridine was cooled to 0 °C and treated dropwise with trifluoromethanesulfonyl anhydride (1.15 eq.). The mixture stirred for 1 h at 20 °C then diluted with H_2O and AcOEt. The organic layer was separated and washed with aqueous HCl (1 N) and brine then dried. Removal of the solvent afforded a residue that was purified by flash chromatography (1:9 AcOEt/petroleum ether eluent) to afford the title compound (64%) as a solid.

^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 3.92 (s, 3H), 7.82 (d, J = 8.7 Hz, 1H), 8.11 (dd, J = 2.2 Hz, J = 8.7 Hz, 1H), 8.17 (d, J = 2.2 Hz, 1H), 11.81 (s, 1H)

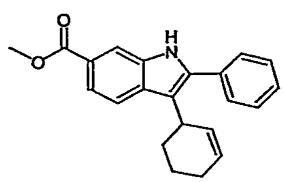


Step 4: methyl 2-phenyl-1*H*-indole-6-carboxylate

A solution (0.3 M) of methyl 3-[(trifluoroacetyl)amino]-4-{[(trifluoromethyl)sulfonyl]oxy}benzoate in dry DMF was treated with

ethynyl benzene (2.0 eq.), tetramethyl guanidine (10.0 eq.), $PdCl_2(PPh_3)_2$ (0.1 eq.) and CuI (0.1 eq.). The mixture was stirred at 20 °C for 1 h then heated at 100 °C for 8 h. The cooled solution was diluted with Et_2O and filtered through Celite. The filtrate was washed with aqueous HCl (1 N) and brine then dried. Removal of the solvent afforded a residue that was purified by flash chromatography (1:9 AcOEt/petroleum ether eluent) to afford the title compound (39%) as a solid.

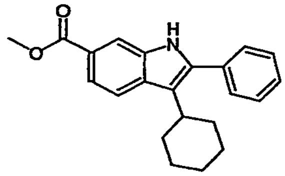
^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 3.88 (s, 3H), 7.04 (s, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.65 (s, 2H), 7.92 (d, J = 7.6 Hz, 2H), 8.08 (s, 1H), 11.94 (s, 1H)



Step 5: methyl 3-cyclohex-2-en-1-yl-2-phenyl-1*H*-indole-6-carboxylate

A solution (0.06 M) of methyl 2-phenyl-1*H*-indole-6-carboxylate in dry DMF was cooled to 0 °C and treated with NaH (1.1 eq.). The mixture was warmed to 20 °C and stirred for 0.5 h, then cooled to 0 °C. A solution (0.3 M) 3-bromocyclohexene (1.3 eq.) in DMF was added dropwise and the mixture was stirred for 2 h at 20 °C. Aqueous HCl (1 N) and AcOEt were added and the organic layer was separated, washed with brine and dried. Removal of the solvent afforded a residue that was purified by flash chromatography on silica gel (1:9 AcOEt/petroleum ether) to afford the title compound (79%) as a solid.

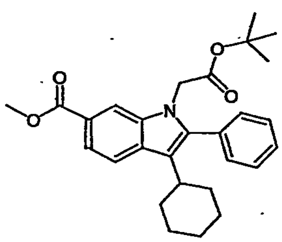
^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 1.57-1.74 (m, 1H), 1.82-2.05 (m, 3H), 2.06-2.18 (m, 1H), 2.18-2.32 (m, 1H), 3.67-3.81 (m, 1H), 3.87 (s, 3H), 5.69 (d, J = 10.4 Hz, 1H), 5.82-5.92 (m, 1H), 7.44-7.52 (m, 1H), 7.54-7.63 (m, 5H), 7.68 (d, J = 8.4 Hz, 1H), 8.03 (s, 1H), 11.59 (s, 1H).



Step 6: methyl 3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate

A solution (0.01 M) of methyl 3-cyclohex-2-en-1-yl-2-phenyl-1*H*-indole-6-carboxylate in MeOH was treated with 10% Pd/C (10% wt.). The resulting suspension was stirred for 12 h under an atmosphere of hydrogen then purged with nitrogen and filtered. The filtrate was concentrated to afford the title compound (91%) as a solid.

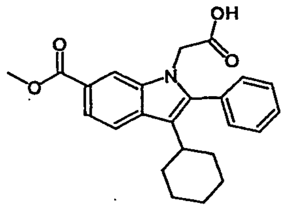
^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 1.21-1.45 (m, 3H), 1.67-1.90 (m, 5H), 1.91-2.11 (m, 2H), 2.82-2.99 (m, 1H), 3.88 (s, 3H), 7.43-7.52 (m, 1H), 7.54-7.60 (m, 4H), 7.62 (dd, J = 1.4 Hz, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 1.4 Hz, 1H), 11.51 (s, 1H).



Step 7: methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate

A solution (0.05 M) of methyl 3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate in DMF was treated with NaH (1.4 eq.) then stirred for 0.5 h. *tert*-Butyl bromoacetate (2.0 eq.) was added dropwise, and the mixture was heated at 50 °C for 12 h. After cooling to room temperature the solution was diluted with AcOEt and washed sequentially with aqueous HCl (1 N) and brine. The dried organic phase was concentrated to give a residue that was purified by flash chromatography on silica gel (5:95 AcOEt/petroleum ether) to afford the title compound (83%) as a solid.

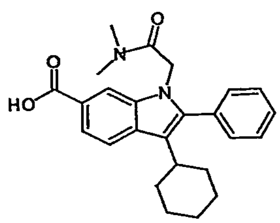
^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 1.19-1.27 (m, 3H), 1.32 (s, 9H), 1.62-1.95 (m, 7H), 2.59-2.67 (m, 1H), 3.89 (s, 3H), 4.75 (s, 2H), 7.33-7.37 (m, 2H), 7.54-7.57 (m, 3H), 7.71 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 8.09 (s, 1H).



Step 8: [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid

A solution (0.07 M) of methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate in a 1:1 (v/v) mixture of CH_2Cl_2/TFA was stirred for 4 h then concentrated under reduced pressure. The residue was triturated with Et_2O to afford the title compound (98%) as a solid.

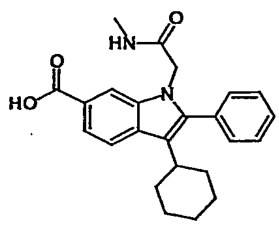
^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 1.17-1.29 (m, 3H), 1.63-1.75 (m, 5H), 1.68-1.90 (m, 2H), 2.51-2.60 (m, 1H), 3.86 (s, 3H), 4.73 (s, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.51-7.56 (m, 3H), 7.68 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 8.02 (s, 1H), 12.96 (br s, 1H).



Step 9: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid

A solution (0.04 M) of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid in DMF was treated with dimethylamine hydrochloride (1.0 eq.) and HATU (1.0 eq.). DIEA (3.0 eq.) was added and the mixture was stirred for 12 h. The mixture was diluted with AcOEt then washed sequentially with aqueous HCl (1 N), saturated aqueous $NaHCO_3$ and brine. The dried organic layer was concentrated and diluted to with CH_2Cl_2. The resulting solution (0.03 M) was treated dropwise with BBr_3 (3 eq.) then stirred for 2 h. The solvent was removed under reduced pressure and the residue was treated with aqueous HCl (1 N) then filtered. Purification by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 100 mm; mobile phase: linear gradient from 40% to 100% MeCN (containing 0.1% TFA) in H_2O (containing 0.1% TFA) over 11 min) gave the title compound (70%) as a solid.

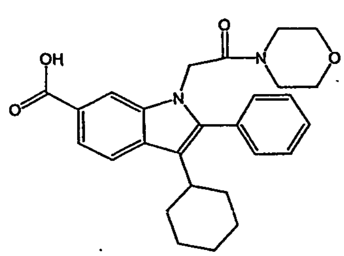
^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 1.13-1.30 (m, 3H), 1.63-1.75 (m, 5H), 1.80-1.90 (m, 2H), 2.53-2.59 (m, 1H), 2.79 (s, 3H), 2.89 (s, 3H), 4.84 (s, 2H), 7.31 (d, J = 6.4 Hz, 2H), 7.48-7.53 (m, 3H), 7.64 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H,); MS (ES$^+$) m/z 405 (M+H)$^+$



Example 8: 3-cyclohexyl-1-[2-(methylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid with methylamine hydrochloride gave a residue that was purified by SPE (stationary phase: Isolute C_{18} 20g; mobile phase: 10% to 60% MeCN in H_2O) to afford the title compound (51%) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 1.16-1.30 (m, 3H), 1.63-1.73 (m, 5H), 1.80-1.89 (m, 2H), 2.51-2.55 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 4.51 (s, 2H), 7.38 (d, J = 6.4 Hz, 2H), 7.48-7.52 (m, 3H), 7.66 (d, J = 8.4 Hz, 1H), 7.8 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.98 (d, J = 4.4 Hz, 1H); MS (ES$^+$) m/z 391 (M+H)$^+$

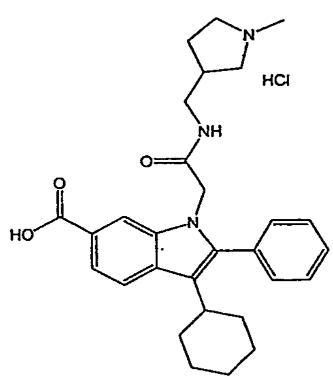


Example 9: 3-cyclohexyl-1-(2-morpholin-4-yl-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of [3-cyclohexyl-

6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid with morpholine (1.2 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 100 mm; mobile phase: linear gradient from 30% to 100% MeCN (containing 0.1% TFA) in H_2O (containing 0.1% TFA) over 10 min) to afford the title compound (66%) as a solid.

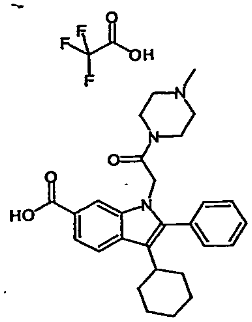
^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 1.17-1.30 (m, 3H), 1.63-1.77 (m, 5H), 1.80-1.90 (m, 2H), 2.53-2.58 (m, 1H), 3.31-3.39 (m, 8H), 4.89 (s, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.49-7.54 (m, 3H), 7.65 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H); MS (ES$^+$) m/z 447 (M+H)$^+$



Example 10: 3-cyclohexyl-1-(2-{[(1-methylpyrrolidin-3-yl)methyl]amino}-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid hydrochloride

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid with 1-(1-methylpyrrolidin-3-yl)methanamine (1.2 eq.) gave a residue that was purified by SPE (stationary phase: Isolute C_{18} 20g; mobile phase: 10% to 70% MeCN in H_2O) to afford the title compound (47%) as a solid.

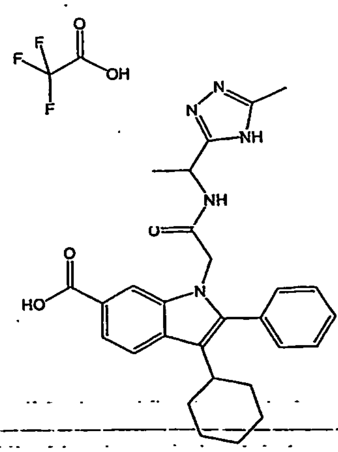
^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 1.17-1.30 (m, 4H), 1.41-1.50 (m, 1H), 1.63-1.78 (m, 5H), 1.82-1.91 (m, 3H), 2.30-2.39 (m, 1H), 2.45 (s, 3H), 2.53-2.58 (m, 1H), 2.67-2.90 (m, 3H), 3.07-3.09 (m, 2H), 4.54 (s, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.49-7.54 (m, 3H), 7.66 (d, J = 8.4 Hz, 3H), 7.83 (d, J = 8.4 Hz, 3H), 7.93 (s, 1H), 8.25 (t, J = 6.0 Hz, 1H); MS (ES$^+$) m/z 474 (M+H)$^+$



Example 11: 3-cyclohexyl-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid trifluoroacetate

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid with 1-methylpiperazine (1.2 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 100 mm; mobile phase: linear gradient from 10% to 100% MeCN (containing 0.1% TFA) in H_2O (containing 0.1% TFA) over 10 min) to afford the title compound (38%) as a solid.

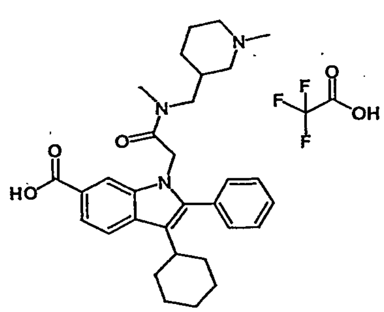
^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 1.17-1.35 (m, 3H), 1.63-1.73 (m, 5H), 1.80-1.89 (m, 2H), 2.53-2.60 (m, 1H), 2.81 (s, 3H), 2.70-2.97 (m, 4H), 3.18-3.42 (m, 2H), 3.97-4.11 (m, 1H), 4.31-4.40 (m, 1H), 4.88-5.12 (m, 2H), 7.30 (d, J = 6.8 Hz, 2H), 7.50-7.55 (m, 3H), 7.66 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 9.88 (br s, 1H), 12.50 (br s, 1H); MS (ES$^+$) m/z 460 $(M+H)^+$



Example 12: 3-cyclohexyl-1-(2-{[1-(5-methyl-4*H*-1,2,4-triazol-3-yl)ethyl]amino}-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid trifluoroacetate

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid with 1-(5-methyl-4*H*-1,2,4-triazol-3-yl)ethanamine dihydrochloride (1.2 eq.) and DIEA (5.0 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 100 mm; mobile phase: linear gradient from 10% to 90% MeCN (containing 0.1% TFA) in H_2O (containing 0.1% TFA) over 10 min) to afford the title compound (46%) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 1.15-1.30 (m, 3H), 1.36 (d, J = 6.8 Hz, 3H), 1.63-1.73 (m, 5H), 1.82-1.90 (m, 2H), 2.34 (s, 3H), 2.53-2.60 (m, 1H), 4.57-4.63 (m, 2H), 4.94-4.98 (m, 1H), 7.36 (d, J = 6.4 Hz, 1H), 7.47-7.51 (m, 3H), 7.65 (d, J = 8.4 Hz, 3H), 7.82 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 8.61 (d, J = 8.0 Hz, 1H); MS (ES$^+$) m/z 486 $(M+H)^+$

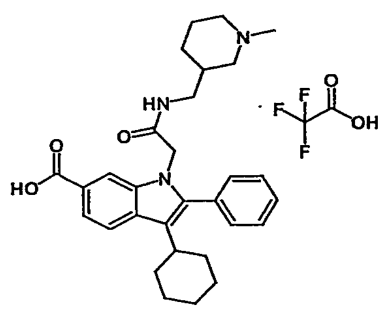


Example 13: 3-cyclohexyl-1-(2-{methyl[(1-methylpiperidin-3-yl)methyl]amino}-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid trifluoroacetate

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of a solution (0.03 M) of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid in CH_2Cl_2 with *N*-methyl-1-(1-methylpiperidin-3-yl)methanamine (1.2 eq.), HATU (2.0 eq.) and DIEA (6.0 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 50 mm; mobile phase: linear gradient from

10% to 90% MeCN (containing 0.1% TFA) in H_2O (containing 0.1% TFA) over 5.5 min) to afford the title compound (51%) as a solid.

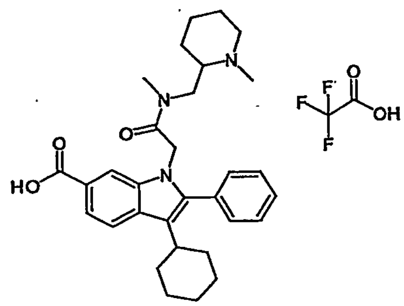
^{1}H NMR (300 MHz, DMSO-d_6, 340 K) δ 1.13-1.41 (m, 3H), 1.47-1.97 (m, 11H), 1.97-2.19 (m, 1H), 2.57-2.71 (m, 1H), 2.78 (s, 3H), 2.94 (s, 3H), 3.04-3.36 (m, 6H), 4.92 (s, 2H), 7.33- 7.50 (m, 2H), 7.53-7.65 (m, 3H), 7.73 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 8.00 (br s, 1H); MS (ES$^+$) m/z 502 $(M+H)^+$



Example 14: 3-cyclohexyl-1-(2-{[(1-methylpiperidin-3-yl)methyl]amino}-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid trifluoroacetate

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of a solution (0.03 M) of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid in CH_2Cl_2 with 1-(1-methylpiperidin-3-yl)methanamine (1.2 eq.), HATU (2.0 eq.) and DIEA (6.0 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 50 mm; mobile phase: linear gradient from 10% to 90% MeCN (containing 0.1% TFA) in H_2O (containing 0.1% TFA) over 5.5 min) to afford the title compound (57%) as a solid.

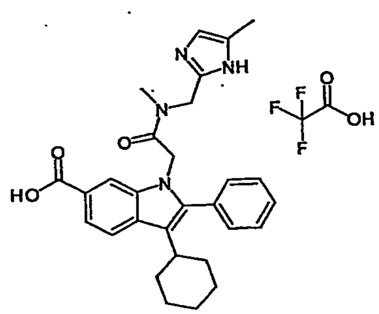
^{1}H NMR (300 MHz, DMSO-d_6, 340 K) δ 0.98-1.40 (m, 5H), 1.48-2.04 (m, 12H), 2.57-2.70 (m, 1H), 2.84 (s, 3H), 2.97-3.11 (m, 2H), 3.17-3.50 (m, 2H), 4.59 (s, 2H), 7.39- 7.49 (m, 2H), 7.50-7.61 (m, 3H), 7.71 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.99 (s, 1H), 8.06 (t, J =5.0 Hz, 1H), 9.15 (br s, 1H); MS (ES$^+$) m/z 488 $(M+H)^+$



Example 15: 3-cyclohexyl-1-(2-{methyl[(1-methylpiperidin-2-yl)methyl]amino}-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid trifluoroacetate

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of a solution (0.03 M) of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid in CH_2Cl_2 with *N*-methyl-1-(1-methylpiperidin-2-yl)methanamine (1.2 eq.), HATU (2.0 eq.) and DIEA (6.0 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 50 mm; mobile phase: linear gradient from 10% to 90% MeCN (containing 0.1% TFA) in H_2O (containing 0.1% TFA) over 5.5 min) to afford the title compound (57%) as a solid.

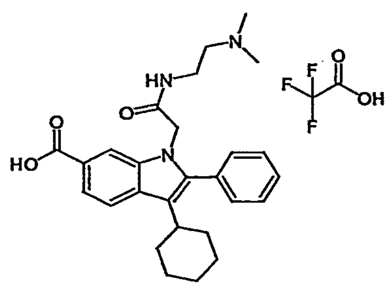
^{1}H NMR (300 MHz, DMSO-d_6, 340 K) δ 1.12-1.42 (m, 5H), 1.54-1.98 (m, 12H), 2.57-2.70 (m, 1H), 2.79 (s, 3H), 2.96 (s, 3H), 3.11-3.83 (m, 4H), 4.93 (s, 2H), 7.30- 7.45 (m, 2H), 7.47-7.61 (m, 3H), 7.69 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H); MS (ES$^+$) m/z 502 $(M+H)^+$



Example 16: 3-cyclohexyl-1-(2-{methyl[(5-methyl-1*H*-imidazol-2-yl)methyl]amino}-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid trifluoroacetate

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of a solution (0.03 M) of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid in CH_2Cl_2 with *N*-methyl-1-(5-methyl-1*H*-imidazol-2-yl)methanamine (1.2 eq.), HATU (2.0 eq.) and DIEA (6.0 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 50 mm; mobile phase: linear gradient from 10% to 90% MeCN (containing 0.1% TFA) in H_2O (containing 0.1% TFA) over 5.5 min) to afford the title compound (65%) as a solid.

^{1}H NMR (300 MHz, DMSO-d_6, 340 K) δ 1.08-1.39 (m, 3H), 1.55-1.99 (m, 7H), 2.28 (s, 3H), 2.52-2.68 (m, 1H), 3.02 (s, 3H), 4.62 (s, 2H), 4.93 (s, 2H), 7.11- 7.39 (m, 3H), 7.41-7.60 (m, 3H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.99 (s, 1H); MS (ES$^+$) *m/z* 485 (M+H)$^+$

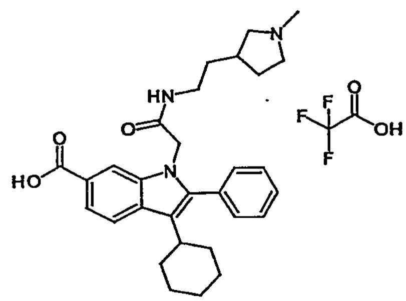


Example 17: 3-cyclohexyl-1-(2-{[2-(dimethylamino)ethyl]amino}-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid trifluoroacetate

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of a solution (0.03 M) of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid in CH_2Cl_2 with *N,N*-dimethylethane-1,2-diamine (1.2 eq.), HATU (2.0 eq.) and DIEA (6.0 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 50 mm; mobile phase: linear gradient from 10% to 90% MeCN (containing 0.1% TFA) in H_2O (containing 0.1% TFA) over 5.5 min) to afford the title compound (63%) as a solid.

^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 1.06-1.45 (m, 3H), 1.56-2.03 (m, 7H), 2.51-2.65 (m, 1H), 2.80 (d, *J* = 4.6 Hz, 6H), 3.04-3.19 (m, 2H), 3.35-3.49 (m, 2H), 4.63 (s, 2H), 7.33- 7.45 (m, 2H), 7.61-7.48 (m, 3H), 7.69 (d, *J*

= 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 8.38 (t, J = 5.4 Hz, 1H), 9.38 (br s, 1H), 12.60 (br s, 1H); MS (ES+) m/z 448 $(M+H)^+$

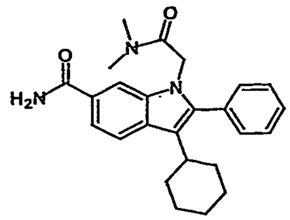


Example 18: 3-cyclohexyl-1-(2-{[2-(1-methylpyrrolidin-3-yl)ethyl]amino}-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid trifluoroacetate

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of a solution (0.03 M) of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid in CH_2Cl_2 with 2-(1-methylpyrrolidin-3-yl)ethanamine (1.2 eq.), HATU (2.0 eq.) and DIEA (6.0 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 50 mm; mobile phase: linear gradient from 10% to 90% MeCN (containing 0.1% TFA) in H_2O (containing 0.1% TFA) over 5.5 min) to afford the title compound (64%) as a solid.

^1H NMR (300 MHz, DMSO-d_6, 300 K) δ 1.04-1.45 (m, 3H), 1.48-2.13 (m, 13H), 2.14-2.35 (m, 1H), 2.54-2.70 (m, 1H) 2.80 (d, J = 4.9 Hz, 3H), 2.97-3.30 (m, 3H), 3.49-3.68 (m, 1H), 4.59 (s, 2H), 7.36-7.48 (m, 2H), 7.50-7.61 (m, 3H), 7.70 (dd, J = 8.4 Hz, J = 1.1 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 1.1 Hz, 1H), 8.28 (t, J =5.6 Hz, 1H), 9.39 (br s, 1H), 12.64 (br s, 1H); MS (ES+) m/z 488 $(M+H)^+$

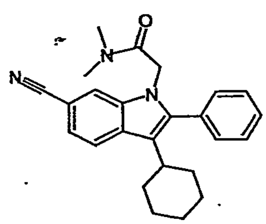
Example 19: 2-[3-cyclohexyl-2-phenyl-6-(1*H*-tetraazol-5-yl)-1*H*-indol-1-yl]-*N*,*N*-dimethylacetamide



Step 1: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxamide

A solution (0.15 M) of 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (prepared as described in example 8) in DMF was treated with pyridine (0.67 eq.), NH_4HCO_3 (1.45 eq.) and di-*tert*-butyl dicarbonate (1.5 eq.). The mixture was stirred for 72 h then diluted with aqueous HCl (1 N) and AcOEt. The organic phase was separated, washed with brine and dried. Removal of the solvent afforded the title compound (67%) as a solid.

^{1}H NMR (600 MHz, DMSO-d_6, 300 K) δ 1.14-1.36 (m, 3H), 1.61-1.79 (m, 5H), 1.81-1.93 (m, 2H), 2.51-2.60 (m, 1H), 2.81 (s, 3H), 2.92 (s, 3H), 4.80 (s, 2H), 7.20 (br s, 1H), 7.31 (d, J = 7.1 Hz, 2H), 7.45-7.54 (m, 3H), 7.60 (s, J = 8.5 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.86 (br s, 1H), 7.87 (s, 1H); MS (ES$^+$) m/z 404 (M+H)$^+$

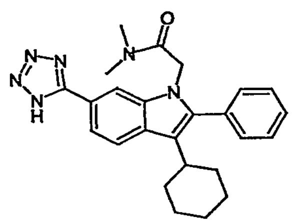


Step 2: 2-(6-cyano-3-cyclohexyl-2-phenyl-1*H*-indol-1-yl)-*N,N*-dimethylacetamide

A solution (0.04 M) of 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxamide in CH_2Cl_2 was treated with triethylamine (6.4 eq.) and then cooled to 0 °C. Trifluoroacetic anhydride was (3.2 eq.) was added dropwise and the mixture was warmed to 20 °C. After 1 h the solvent was removed and the residue was taken up in AcOEt and aqueous HCl (1 N). The organic layer was separated, washed with brine and dried. Removal of the solvent gave a residue that was purified by flash

chromatography on silica gel (1:9 AcOEt/petroleum ether) to afford the title compound (90%) as a solid.

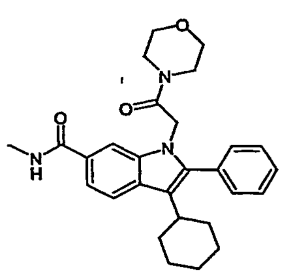
^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 1.08-1.40 (m, 3H), 1.58-1.97 (m, 7H), 2.51-2.65 (m, 1H), 2.80 (s, 3H), 2.90 (s, 3H), 4.87 (s, 2H), 7.28-7.36 (m, 2H), 7.38 (dd, *J* = 8.4 Hz, *J* = 1.2 Hz, 2H), 7.48-7.61 (m, 3H), 7.94 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 1.2 Hz, 1H); MS (ES$^+$) *m/z* 386 (M+H)$^+$



<u>*Step 3*: 2-[3-cyclohexyl-2-phenyl-6-(1*H*-tetraazol-5-yl)-1*H*-indol-1-yl]-*N,N*-dimethylacetamide</u>

A solution (0.02 M) of 2-(6-cyano-3-cyclohexyl-2-phenyl-1*H*-indol-1-yl)-*N,N*-dimethylacetamide in toluene was treated with Bu_3SnN_3 (2.0 eq.) and the mixture was heated under reflux for 24 h. The cooled solution was diluted with AcOEt and washed with aqueous HCl (1 N) and then brine. The organic phase was dried and concentrated, and the residue was triturated with pentane to afford a yellow solid. Purification of this material by HPLC (stationary phase: Waters X-terra C_{18} 19mm x 100 mm) afforded the title compound (45%) as a solid.

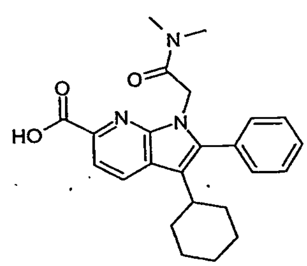
^{1}H NMR (600 MHz, DMSO-d_6, 300 K) δ 1.14-1.27 (m, 2H), 1.27-1.38 (m, 1H), 1.62-1.70 (m, 1H), 1.70-1.81 (m, 4H), 1.83-1.96 (m, 2H), 2.55-2.63 (m, 1H), 2.82 (s, 3H), 2.93 (s, 3H), 4.86 (s, 2H), 7.33 (d, *J* = 6.6 Hz, 2H), 7.38 (dd, *J* = 8.4 Hz, *J* = 1.2 Hz, 1H), 7.46-7.57 (m, 3H), 7.70 (d, *J* = 8.2 Hz, 1H), 8.97 (d, *J* = 8.2 Hz, 1H), 8.00 (s, 1H); MS (ES$^+$) *m/z* 429 (M+H)$^+$



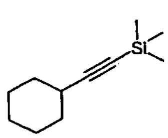
Example 20: 3-cyclohexyl-*N*-methyl-1-(2-morpholin-4-yl-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxamide

A solution (0.02 M) of 3-cyclohexyl-1-(2-morpholin-4-yl-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid (prepared as described in example 10) in CH_2Cl_2 was treated with methylamine hydrochloride (1.2 eq.) and HATU (2.0 eq.). DIEA (6.0 eq.) was added and the mixture was stirred for 12 h. The mixture was diluted with CH_2Cl_2 then washed sequentially with aqueous HCl (1 N), aqueous NaOH (1 N) and brine. The dried organic layer was concentrated and the residue was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19 mm x 100 mm) to afford the title compound (35%) as a solid.

^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 1.20-1.38 (m, 3H), 1.70-1.80 (m, 5H), 1.86-1.98 (m, 2H), 2.34 (s, 3H), 2.58-2.68 (m, 1H), 2.88 (d, J = 4.5 Hz, 3H), 3.40-3.54 (m, 6H), 3.55-3.60 (m, 2H), 4.89 (s, 2H), 7.37 (d, J =5.7 Hz, 2H), 7.53-7.62 (m, 4H), 7.84 (d, J = 8.4 Hz, 1H), 7.91 (s, 1H), 8.33 (d, J = 4.5 Hz, 1H); MS (ES$^+$) m/z 460 $(M+H)^+$



Example 21: 3-cyclohexyl-1- [2-(dimethylamino)-2-oxoethyl]-2-phenyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid

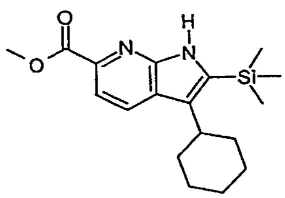


Step 1: (cyclohexylethynyl)(trimethyl)silane

A solution (0.16 M) of 2,2,2-trichloro-1-cyclohexylethyl 4-methylbenzenesulfonate (obtained as described in *J. Org. Chem.*, **65**, 1889-1891, 2000) was cooled to -10 °C and a solution of MeLi (1.6 M) was added *via* dropping funnel keeping the temperature below -5 °C. After the addition the temperature was raised to room temperature over 1 h then the mixture was cooled to –78 °C and treated with TMSCl

(1.7 eq.). After warming to 0 °C the reaction was quenched with saturated aqueous NH_4Cl solution and Et_2O. The organic layer was separated and washed with brine then dried and concentrated to give a crude material which was submitted to fractional distillation. The title compound (63%) distilled off as colorless liquid at 80-82 °C/ 15-17 mbar.

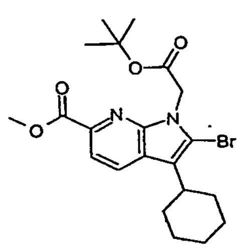
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) 0.33 (s, 9H), 1.14-1.49 (m, 6H), 1.62-1.82 (m, 4H), 2.30- 2.41 (m, 1H)



Step 2: methyl 3-cyclohexyl-2- (trimethylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate

To a solution (0.1 M) of methyl 6-amino-5-bromo-2-pyridinecarboxylate (obtained as described in *J. Org. Chem.*, **61**, 4623-4633, 1996) in DMF were added (cyclohexylethynyl)(trimethyl)silane (obtained as described in step 1) (3 eq.), LiCl (1 eq.), Na_2CO_3 (2 eq.) and Pd(dppf)Cl_2 (0.1 eq.). The suspension was heated at 110 °C for 15 h under argon, then diluted with AcOEt and H_2O and filtered through celite. The organics were washed with H_2O and dried, then concentrated and purified by flash chromatography on silica gel (AcOEt/petroleum ether) to afford the title compound (60%) as a pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ 0.39 (s, 9H), 1.39 (m, 3H), 1.82-1.90 (m, 7H), 2.75-2.90 (m, 1H), 4.02 (s, 3H), 7.89 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 8.53 (br s, 1H); MS (ES$^+$) m/z 331 (M+H)$^+$

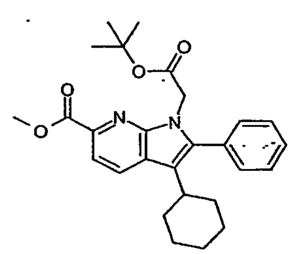


***Step 3*: methyl 2-bromo-1- (2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate**

To a solution (0.15 M) of methyl 3-cyclohexyl-2- (trimethylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate (obtained as described in step 2) in DMF was added NaH (1.2 eq.) and the suspension was heated at 40 °C for 15 min under nitrogen. To the resulting clear solution *tert*-butyl bromoacetate (1.3 eq.) was added and the mixture was stirred at 60 °C for 45 min. The reaction was cooled to room temperature, diluted with AcOEt and washed with water, brine, dried and concentrated to give methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate as a pale orange solid.

MS (ES^+) *m/z* 373 $(M+H)^+$. A solution (0.10 M) of this crude material in CH_2Cl_2 was treated with NBS (1.2 eq.) then stirred at 20 °C for 1 h. The solution was diluted with AcOEt and washed with saturated aqueous $Na_2S_2O_3$ solution and brine then dried, concentrated and purified by flash chromatography on silica gel (AcOEt /petroleum ether) to afford the title compound (50%) as a white solid.

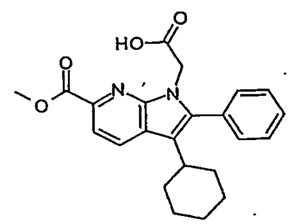
^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 1.40-1.46 (m, 2H), 1.47 (s, 9H), 1.81-1.92 (m, 8H), 2.88-2.97 (m, 1H), 4.01 (s, 3H), 5.11 (s, 2H), 7.91 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H); MS (ES^+) *m/z* 451 $(M+H)^+$



***Step 4*: methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate**

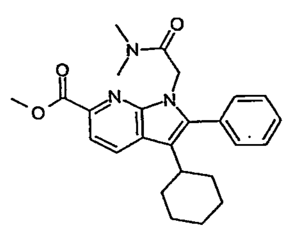
To a solution (0.08 M) of methyl 2-bromo-1- (2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate (obtained as described in step 3) in toluene were added phenylboronic acid (1.5 eq.), potassium phosphate (1.2 eq.), $Pd(PPh_3)_4$ (0.5 eq.) and the suspension was heated at 110 °C overnight under argon. After cooling to room temperature, the solvent was removed and the residue dissolved in AcOEt and washed with H_2O, brine, dried, concentrated and purified by flash

chromatography on silica gel (AcOEt/petroleum ether) to afford the title compound (60%) as a pale yellow solid.
^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 1.30-1.33 (m, 2H), 1.33 (s, 9H), 1.79-1.85 (m, 8H), 2.61-2.72 (m, 1H), 4.01 (s, 3H), 4.88 (s, 2H), 7.37-7.51 (m, 5H), 7.95 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H); MS (ES^+) m/z 449 $(M+H)^+$



Step 5: **[3-cyclohexyl-6- (methoxycarbonyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]acetic acid**

A solution (0.06 M) of methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate (obtained as described in step 4) in CH_2Cl_2/TFA (1:1, v/v) was stirred at room temperature for 1 h. The solvent was removed to afford the title compound (100%) as a yellow solid.
^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 1.28-1.33 (m, 2H), 1.68-1.82 (m, 8H), 2.61-2.72 (m, 1H), 4.00 (s, 3H), 4.88 (s, 2H), 7.40-7.55 (m, 5H), 7.96 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H); MS (ES^+) m/z 393 $(M+H)^+$

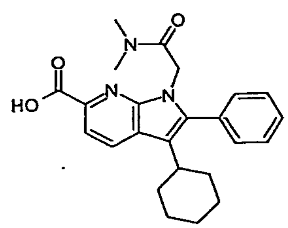


Step 6: **methyl 3-cyclohexyl-1- [2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate**

To a solution (0.05 M) of [3-cyclohexyl-6- (methoxycarbonyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]acetic acid (obtained as described in step 5) in DMF were added dimethylamine hydrochloride (1.1 eq.), HATU (1.2 eq.), DIEA (3.5 eq.) and the solution was stirred at room temperature under nitrogen for 1.5 h. The solution was diluted with AcOEt and washed with aqueous HCl (1 N), aqueous NaOH (1 N) and

brine then dried and concentrated to afford the title compound (100%) as a yellow solid.

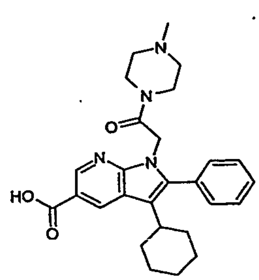
^1H NMR (400 MHz, $CDCl_3$, 300 K) δ 1.28-1.33 (m, 2H), 1.72-1.90 (m, 8H), 2.62-2.68 (m, 1H), 2.88 (s, 3H), 3.02 (s, 3H), 4.01 (s, 3H), 4.97 (s, 2H), 7.43-7.51 (m, 5H), 7.93 (d, J = 8.2 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H); MS m/z (ES^+) 420 $(M+H)^+$



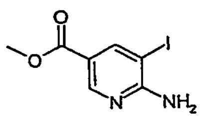
Step 7: **3-cyclohexyl-1- [2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylic acid**

To a solution (0.02 M) of methyl 3-cyclohexyl-1- [2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate (obtained as described in step 6) in CH_2Cl_2 was added neat BBr_3 (3.0 eq.) and the solution was stirred at room temperature under nitrogen for 30 min. The solvent was removed and the residue treated with aqueous HCl (1 N) and purified by preparative HPLC (mobile phase: $MeCN/H_2O$ containing 0.1% TFA) to afford the title compound (45%) as a yellow solid.

^1H NMR (400 MHz, DMSO-d_6, 300 K) δ 1.16-1.35 (m, 3H), 1.63-1.88 (m, 7H), 2.53-2.63 (m, 1H), 2.74 (s, 3H), 2.94 (s, 3H), 4.99 (s, 2H), 7.38-7.58 (m, 5H), 7.85 (d, J = 8.2 Hz, 1H), 8.32 (d, J = 8.2 Hz, 1H); MS (ES^+) m/z 406 $(M+H)^+$



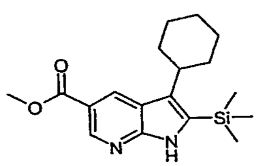
Example 22: 3-cyclohexyl-1- [2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic acid



Step 1: methyl 6-amino-5-iodonicotinate

To a solution (0.48 M) of methyl 6-aminonicotinate in glacial acetic acid/ TFA (20:1, v/v) was added NIS (1.5 eq.) and the solution was stirred at room temperature overnight. To the solution were added ice, saturated aqueous NH_4OH until pH c. 9 was reached. The precipitate was isolated by filtration, dissolved in $CHCl_3$ and washed with saturated aqueous $Na_2S_2O_3$ solution, H_2O and brine then dried and concentrated to afford the title compound (50%) as a solid.

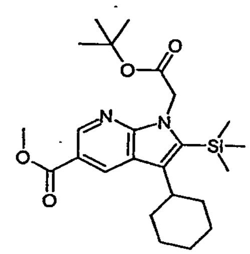
^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 3.77 (s, 3H), 6.90-7.0 (br s, 2H), 8.26 (d, J = 2.0 Hz, 1H), 8.49 (d, J = 2.0 Hz, 1H); MS (ES$^+$) m/z 279 (M+H)$^+$



Step 2: methyl 3-cyclohexyl-2- (trimethylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate

To a solution (0.1 M) of methyl 6-amino-5-iodonicotinate (obtained as described in step 1) in DMF were added (cyclohexylethynyl)(trimethyl)silane (obtained as described in example 21, step 1) (3 eq.), LiCl (1 eq.), Na_2CO_3 (2 eq.) and Pd(dppf)Cl_2 (1 eq.). The suspension was heated in microwave for 10 min at 180 °C, then diluted with AcOEt/H_2O (1/1, v/v) and filtered through celite. The organics were washed with brine and dried then concentrated and purified by flash chromatography on silica gel (AcOEt/petroleum ether) to afford the title compound (20%) as an off-white solid.

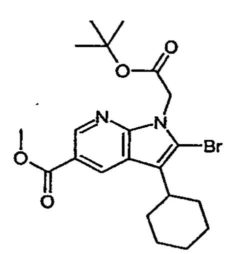
^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 0.39 (s, 9H), 1.37-1.45 (m, 3H), 1.80-1.97 (m, 7H), 2.77- 2.85 (m, 1H), 3.97 (s, 3H), 8.71 (s, 1H), 8.93 (s, 1H), 9.04 (br s, 1H); MS m/z (ES$^+$) 331 (M+H)$^+$



<u>*Step 3*: **methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-2- (trimethylsilyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylate**</u>

To a solution (0.16 M) of methyl 3-cyclohexyl-2- (trimethylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (obtained as described in step 2) in DMF was added NaH (1.2 eq.) and the suspension was heated at 40 °C for 15 min under nitrogen. To the resulting clear solution *tert*-butyl bromoacetate (1.3 eq.) was added and the mixture stirred at 60 °C for 45 min. After cooling the solution was diluted with AcOEt, washed with H_2O and brine then dried, concentrated and purified by flash chromatography on silica gel (AcOEt/petroleum ether) to afford the title compound (60%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 0.39 (s, 9H), 1.37-1.51 (m, 3H), 1.44 (s, 9H), 1.75-1.97 (m, 7H), 2.87-2.98 (m, 1H), 3.95 (s, 3H), 5.08 (s, 2H), 8.66 (d, J = 2.0 Hz, 1H), 8.91 (d, J = 2.0 Hz, 1H); MS (ES$^+$) m/z 447 (M+H)$^+$

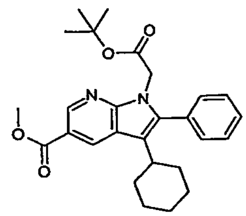


Step 4: methyl 2-bromo-1- (2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate

To a solution (0.1 M) of methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-2-(trimethylsilyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylate (obtained as described in step 3) in CH_2Cl_2 was added NBS (2 eq.) and the solution stirred at room temperature for 1 h. The solution was diluted with AcOEt and washed with saturated aqueous $Na_2S_2O_3$ solution and brine then dried, concentrated and purified by flash

chromatography on silica gel (AcOEt/petroleum ether) to afford the title compound (45%) as a white solid.

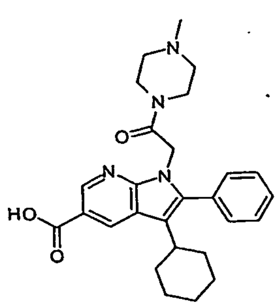
[1]H NMR (400 MHz, $CDCl_3$, 300 K) δ 1.37-1.48 (m, 3H), 1.42 (s, 9H), 1.75-1.93 (m, 7H), 2.85-2.96 (m, 1H), 3.97 (s, 3H), 5.02 (s, 2H), 8.62 (d, J = 2.0 Hz, 1H), 8.90 (d, J = 2.0 Hz, 1H); MS (ES^+) m/z 451 $(M+H)^+$



Step 5: methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate

To a solution (0.08 M) of methyl 2-bromo-1- (2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (obtained as described in step 4) in toluene were added phenylboronic acid (1.5 eq.), potassium phosphate (2 eq.), $Pd(PPh_3)_4$ (0.1 eq.) and the suspension was heated at 110 °C overnight under argon. After cooling, the solvent was removed and the residue was dissolved in AcOEt, washed with H_2O and brine then dried, concentrated and purified by flash chromatography on silica gel (AcOEt/petroleum ether) to afford the title compound (70%) as a colorless oil.

[1]H NMR (300 MHz, $CDCl_3$, 300 K) 1.22 (m, 2H), 1.29 (s, 9H), 1.75- 1.79 (m, 8H), 2.57-2.63 (m, 1H), 3.95 (s, 3H), 4.71 (s, 2H), 7.31- 7.45 (m, 5H), 8.67 (d, J = 2.0 Hz, 1H), 8.92 (d, J = 2.0 Hz, 1H); MS (ES^+) m/z 449 $(M+H)^+$



Step 6: 3-cyclohexyl-1- [2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic acid

A solution (0.05 M) of methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (obtained as described in step 5) in CH_2Cl_2/TFA (1:1, v/v) was stirred at room temperature for 1 h. The solvent was removed to give [3-cyclohexyl-5-(methoxycarbonyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]acetic acid (100%). To a solution (0.09 M) of this material in DMF were added N-methylpiperazine (1.5 eq.), HATU (1.2 eq.), DIEA (3.0 eq.) and the resulting mixture was stirred at room temperature under nitrogen for 1.5 h. The solution was diluted with AcOEt and washed with saturated aqueous NH_4Cl solution, H_2O and brine then dried and concentrated to give methyl 3-cyclohexyl-1- [2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate as a red oil. This material was dissolved in THF (0.18 M) and aqueous KOH (1 N, 3 eq.) was added. The solution was stirred overnight at room temperature then adjusted to pH 3 by addition of aqueous HCl (1 N). The solution was diluted with MeCN/H_2O and purified by preparative HPLC (mobile phase: CH_3CN /H_2O containing 0.1% TFA) to afford the title compound (50%) as a solid.

^{1}H NMR (600 MHz, DMSO-d_6, 300 K) δ 1.19-1.33 (m, 3H), 1.66-1.68 (m, 1H), 1.77-1.82 (m, 6H), 2.59-2.61 (m, 1H), 2.79 (br s, 6H), 4.09-4.27 (m, 2H), 4.97-5.08 (m, 2H), 7.36-7.38 (m, 2H), 7.51-7.56 (m, 3H), 8.63 (d, J = 1.7 Hz, 1H), 8.79 (d, J = 1.7 Hz, 1H), 9.8 (br s, 1H); MS (ES$^+$) m/z 461 (M+H)$^+$

Table 1. Additional Examples (C-6 carboxylic acids)

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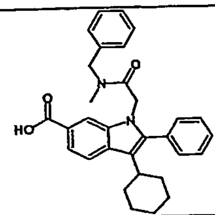
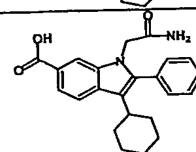
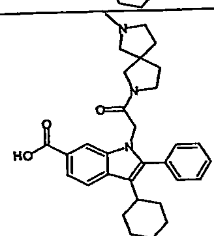
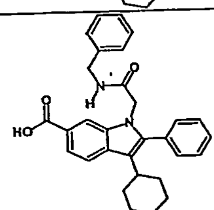
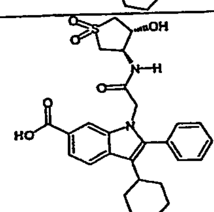
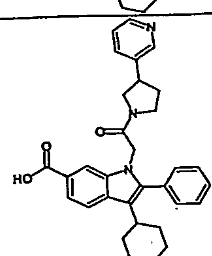
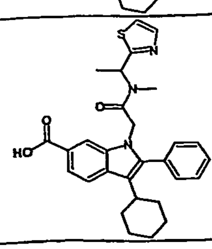
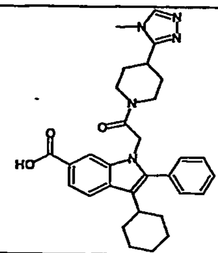
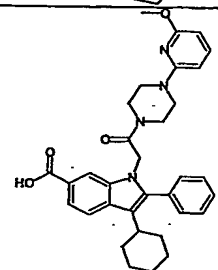
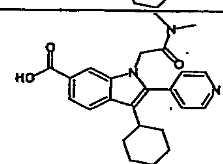
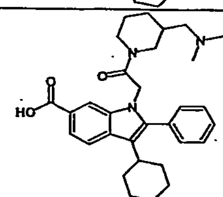
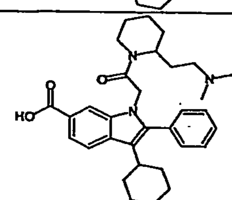
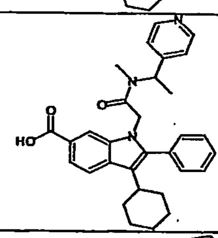
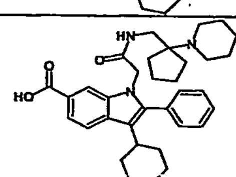
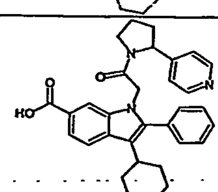
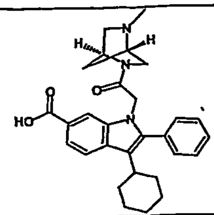
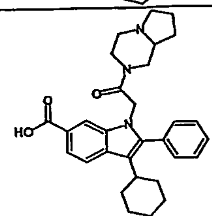
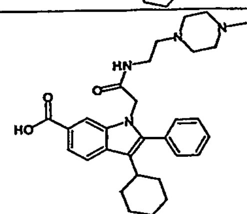
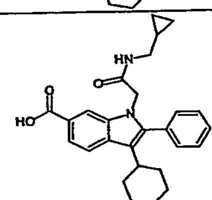
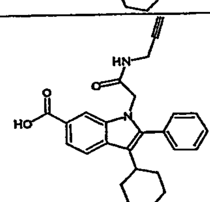
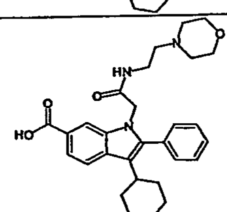
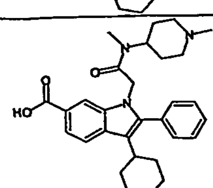
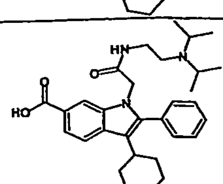
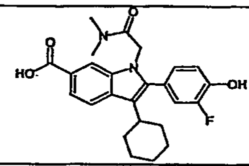
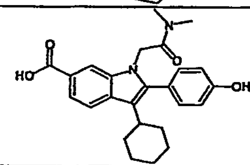
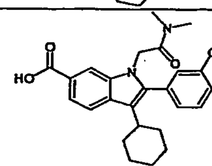
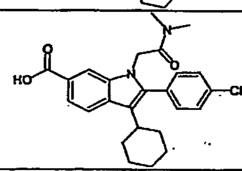
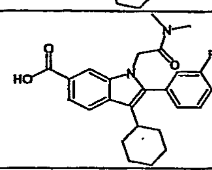
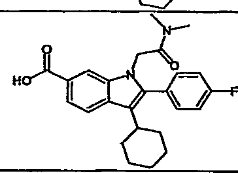
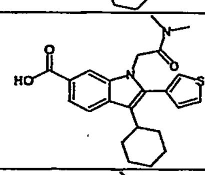
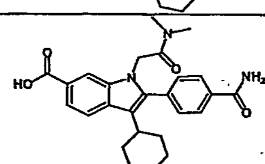
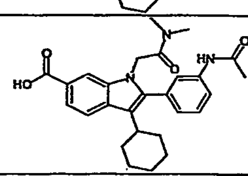
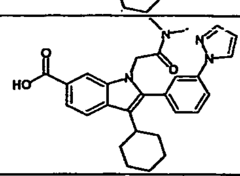
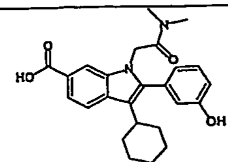
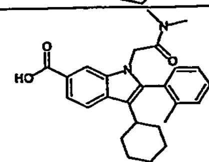
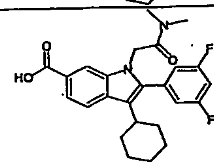
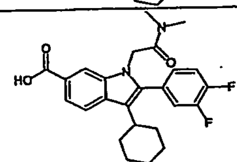
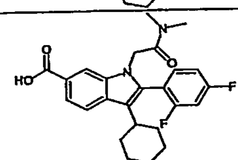
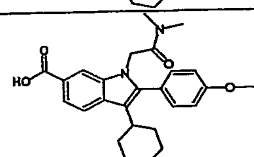
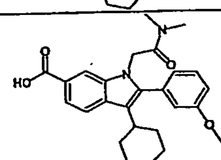
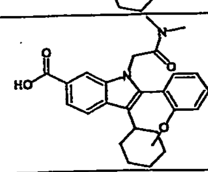
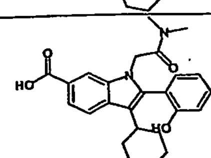
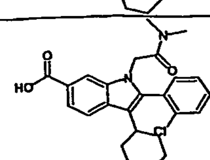
	481
	377
	500
	467
	511
	508
	502

	526
	553
	406
	502
	516
	496
	542
	508

	472
	486
	503
	431
	415
	490
	486
	504

	439
	421
	439
	439
	423
	423
	411
	448
	462
	471

	421
	419
	441
	441
	441
	435
	435
	435
	421
	439

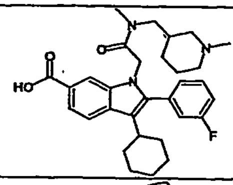
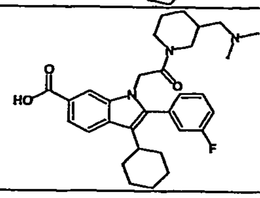
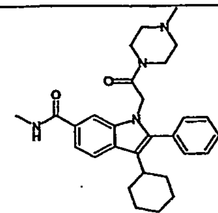
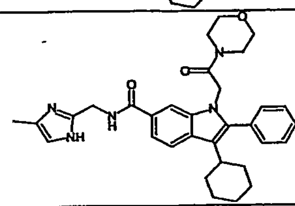
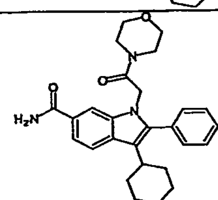
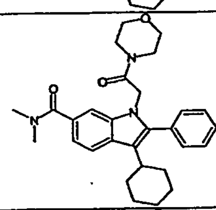
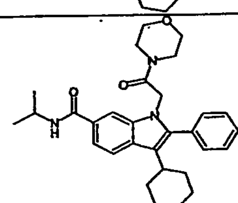
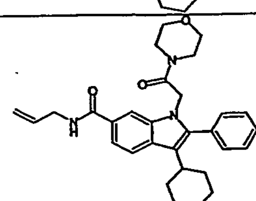
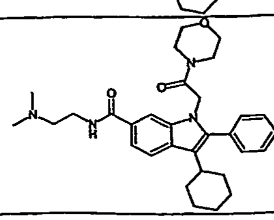
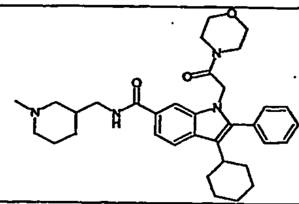
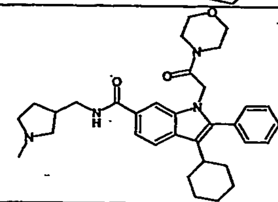
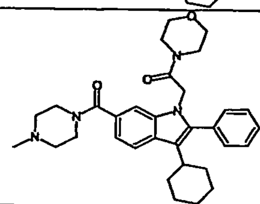
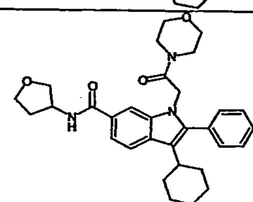
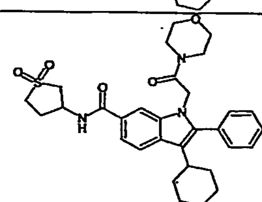
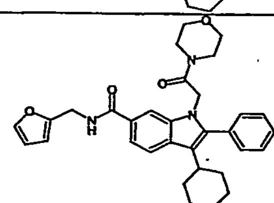
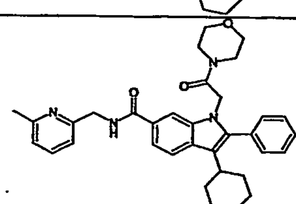
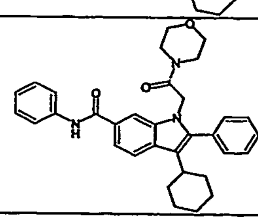
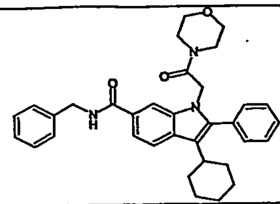
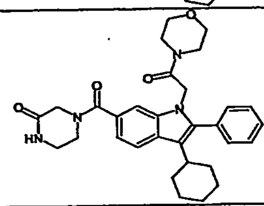
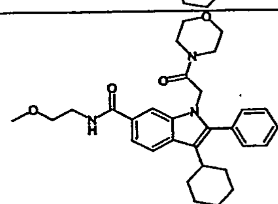
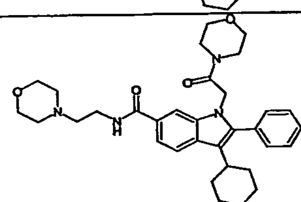
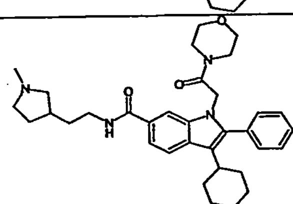
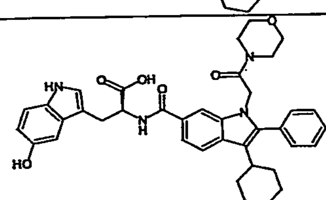
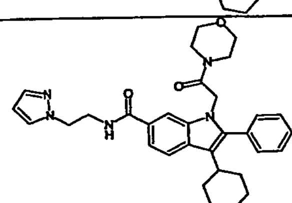
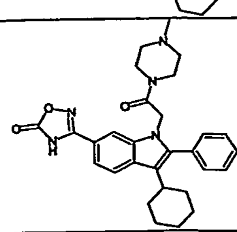
	520
	520

Table 2. Additional Examples (C-6 Carboxamides / Acid Replacements)

STRUCTURE	Moleuclar Ion $[M+H]^+$
	473
	540
	446
	474
	488
	486
	517

	557
	543
	529
	516
	564
	526
	551
	522

	536
	529
	504
	559
	557
	649
	540
	500

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